Stress-related mental disorders with sick leave: a minimal intervention in general practice

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Stress-related mental disorders with sick leave: a minimal intervention in general practice

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Contents

1

Introduction

The reported prevalence of mental health problems in the working population of developed countries ranges from 10 –18 %[1;2] and the prognosis after presentation is far from ideal for about 20% of the patients[3]. Mental health problems often affect functioning to such an extent that they result in sick leave. Furthermore, deterioration of symptoms may lead to chronicity and loss of work[4-6]. Since the comprehensive disability insurance act for employees (WAO) was introduced in the Netherlands in 1967, the number of workers collecting disability benefits has increased from 150,000 to almost one million in the beginning of the new Millennium. Disquietingly, young female employees with mental health problems now constitute the majority of the group of workers who enter the disability benefit system[7]. In up to 90% of the disability benefits paid because of mental health problems, the initial context or cause is stress- related[8-12]. Ever since the introduction of the disability insurance act, there has been a strong and ongoing disability debate in Dutch society and politics. For a long time prevention of work incapacity has played a minor role in employers' and government policies. However, the comparatively high sickness absence rates and large numbers of disability benefit recipients have fostered preventive policies. The Dutch government set up a special committee, which developed a general guideline on how to improve the management of (preventing) sick leave due to mental health problems[13]. The main aspects in this guideline are keeping up regular contacts between employee and employer after sick-leave, early and adequate diagnosis and intervention, and early activation.
Most people having Stress-related Mental Disorders (SMDs) with sick leave consult their general practitioner (GP) at an early stage, and GPs experience two kinds of problems in dealing with SMDs. First, diagnosing SMDs is not always straightforward. It can be difficult to recognize depressive and anxious reactions, and to differentiate between general distress on the one hand, and specific psychiatric and somatic symptoms on the other hand. There is also a substantial and fluctuating overlap between the relevant psychological dimensions and co-morbidity. Second, GPs often do not recognize the patients' tendencies to avoid problems, thereby increasing the risk for prolonged disability.
To set a first step in addressing this important problem form a general practice perspective, we developed a generic Minimal Intervention teaching package to help GPs in the management of Stress-related mental disorders with Sick leave (MISS).

Main concepts

Outline of the setting: GP consulting hours

Pleased to see he was *only* ten minutes behind schedule, Mr Workhard, a GP in Amsterdam, the Netherlands, returned to his desk. He was ready to invite the next patient in. Mrs Braveheart, 34 years old, visits about once a year for a common cold or the flu. Mrs Braveheart entered the room and sat down in front of him, after giving a frail hand, looking away. By a quick look at the electronic medical record system, doctor Workhard saw that 'fatigue' was the given reason for her encountering. "Well, Mrs Braveheart, can you please tell me what is the matter?" he opened the conversation, as he was friendly looking in her direction. "Well, see doctor", she started, "I have been feeling really tired lately. In fact, last week it was only getting worse and I could not pull up with everyone constantly placing requests on me. So, as a result I decided to temporally cancel work, for just a few days, but currently I am still on sick leave because things have not got better yet. And initially my sick leave was quite a relief, but when I think of the huge amount of work that is waiting for me

when I re-enter… It all is very unpleasant and now I hardly sleep at night and in the day I am too tired and stressed out to do anything valuable, like preparing a proper diner for my family. I keep ruminating and worrying about the whole situation I am in and really I don't know what to do". Mrs Braveheart looked agitated and a little helpless as she ended her story.

Medical approach to mental disorders

Historically, a categorical definition of diagnoses has been used to promote communication and define straightforward psychiatric morbidity. Established psychiatric diagnostic schemes such as the Diagnostic and Statistical Manual of Mental Disorders (DSM)[14] and chapter V of the International Statistical Classification of Diseases and Related Health Problems (ICD)[15] were developed to classify the psychological and behavioural diseases found among psychiatric inpatients[16;17]. Definitions of mental disorder typically involve that the pattern of symptoms experienced by an individual adversely affects everyday functioning[18]. The DSM-IV[19] requires that symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The DSM-IV does not conceptually or operationally define the term distress, or impairment[17]. According to the ICD-10[15], a disorder implies the existence of a clinically recognizable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions. Also in the literature distress is referenced frequently, but seldom is defined as a distinct concept. Mostly it is embedded in the context of depression and anxiety.

The DSM and ICD criteria reflect the medical approach, which argues that distress reflects an underlying illness[20], the focus is on diagnosis. Although the scope of the DSM and ICD has broadened with successive revisions, they remain more applicable to patients who are seen by psychiatrists than the much larger proportion who are considered by their GP to have mental health problems. The practice of medicine has changed, and identification and treatment of mental disorders have shifted towards primary care. Yet, there is no necessary conflict between the concepts of mental disorders used by psychiatrists and those used by GPs, but the kind of disorders are somewhat different, and GPs must necessarily work in ways different from those of the psychiatrists[21]. In primary care, psychiatric morbidity seldom separates out into discrete diagnostic entities. It may better be conceptualised as a continuum on a dimensional scale[22], with focus on the context.

So, both categorical systems of DSM and ICD played an important and valuable role in providing a common nomenclature for mental disorders. Subsequently, a number of studies report relevant dimensions of psychopathology, in order to obtain a more comprehensive assessment of psychological morbidity in primary care. The Dimensional model from Goldberg & Huxley [22] was designed on the basis of finding two highly correlated dimensions: anxiety and depression. Subsequently, the tripartite model of Clark & Watson[23] denotes general distress, in addition to depression and anxiety, as a separate dimension. Furthermore, Ormell et all.[24] found three relevant dimensions: next to depression, anxiety was split into generalized anxiety and phobic anxiety. Then, Terluin[25] found 4 relevant dimensions: distress, depression, anxiety, and somatization. He stated that it is important for treatment of mental disorders in general practice to differentiate between general distress on the one hand, and psychiatric symptoms- depression, anxiety and somatization- on the other hand. Last but not least, Clarke[16] found even more relevant dimensions; he added a differentiation in grief and somatic symptoms dimensions and the elaboration of demoralisation. Demoralisation may be viewed as a combination of distress and subjective

incompetence, and it is distinguishable from depression by the absence of anhedonia. As opposed to psychiatric illness, demoralisation is considered to be a normal response to adversity[26].

Sociological approach to mental disorders

Distinct to the medical approach, with its focus on the underlying illness, another approach on mental disorders is sociological of nature. This perspective argues that distress is the consequence of a failure to respond adaptively to social challenge. Here, the focus is on understanding and clarifying patient's dilemma's in their failure to respond adaptively, as opposed to solely a focus on the diagnosis. Distress is described in relation to control and demands[27] and in relation to coping style[28]. Common psychopathology, as seen in primary care, often starts with failure to cope with personal, social or occupational demands. The ability to cope or readjust is overtaxed, and this increases the probability that psychological distress will follow. The importance of work related psychosocial factors to the development of mental disorders is illustrated with Karasek's Demand-Control (DC) model[27]. Moreover, Lazarus and Folkman (1980)[28] define coping responses as cognitions and behaviours that a person uses to reduce stress and to moderate its emotional impact. Their model, the Ways of Coping model (WOC), includes two opposite coping strategies: approach and avoidant coping. Approach coping strategies are either behavioural or psychological responses designed to change the nature of the stressor itself or how one thinks about it, whereas avoidant coping strategies lead people into activities (such as alcohol use) or mental states (such as withdrawal) that keep them from directly addressing stressful events. Approach coping strategies are thought to be better ways to deal with stressful events, and avoidant coping strategies appear to be a psychological risk factor or marker for adverse responses to stressful life events[29].

Treatment of SMDs with sick leave in primary care

There are general practice guidelines available for the treatment of depression[30] and anxiety[31], but these do not cover stress as a separate aspect of the problem or consider functional recovery as an effect-generator for well-being. The care that is provided for SMD patients on sick leave is very heterogeneous and sub-optimal[5]. For a long time the usual approach to SMDs with sick leave was the advice to take rest and not return to work before all complaints had disappeared. Furthermore, GPs are not always aware of the potential harmful consequences of sick leave and stress, because the symptoms seem to be self-limiting. Last but not least, GPs may be overly cautious and not question the continuation of sick leave or ask the patient to take the responsibility and make more effort to cope with the situation, because they may feel that this undermines the mutual trust between patient and doctor[32;33].

Our intervention: the MISS

While depressive disorders and anxiety disorders received much attention and have been studied thoroughly, and it is clear and evidence- based to treat major psychiatric disorders with medication or counselling, evidence- based interventions for the whole range of SMDs are still under development. Taken into account that GPs only have limited time during consulting hours, Terluin and Van der Klink[34] have outlined an activating intervention for patients having a SMD with sick leave, that already proved to be effective in reducing sick

leave by 30% in an occupational health care setting[35]. By using specific communication and the minimal amount of time necessary, the GP helps the patient on the accurate and time-contingent course. The training comprised two sessions of 3.5 hours and 2 regular follow-up sessions of 2 hours (total 11 hours).

Objectives and outline of the thesis

In this thesis, we focus on the diagnosis and treatment of stress-related mental disorders in primary care. In chapter 2, the problems of stress and coping in relation to common mental disorders in general practice patients are described, along with a presentation of our intervention, the MISS. In chapter 3 the setting and design of our study are specified, in order to ascertain the study complies with the requirements for a cluster randomised controlled trial (RCT) as stated by the guidelines in the Consolidated Standards of Reporting Trials (CONSORT)[36]. The main purposes of this study, as presented in chapters 4 and 5, were to assess the effectiveness and cost-effectiveness of our Minimal Intervention for Stress-related mental disorders with Sick leave (MISS) in primary care. Next, as described in chapter 6, we proceeded with a process evaluation to explore the implementation, receipt, and setting of our intervention. We distinguished between components of the intervention and assessed the reach of the intervention. Chapter 7 deals with the test-retest reliability of an instrument that may help to diagnose mental disorders in primary care, the Primary Care Evaluation of Mental Disorders (PRIME-MD), and illustrates some limitations in the current system of diagnosing mental disorders in primary care. Finally, in chapter 8 the findings described in this thesis are discussed, and the implications for general practice and future research are addressed.

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2

Stress-related mental disorders, demoralisation, nervous breakdown, and a minimal intervention to reduce resulting sick leave

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Abstract
Many general practice patients present with common mental disorders. Irrespective whether these disorders are diagnosable or not according to standard psychiatric classifications, most - if not all - of them are stress-related to some extent. Stress results from an imbalance between demands and resources to cope with these demands. A breakdown of coping results in demoralisation. In patients with paid jobs such a “nervous breakdown” leads to sick leave, which is often long-lasting, carrying the risk of social marginalisation due to long-standing mental disability, subsequent loss of employment, and costs. Persistent avoidance is hypothesised to be an important determinant of such a poor outcome. Recovery from a “nervous breakdown” requires that the patients switch from avoiding to actively confronting their problems. We developed a minimal intervention strategy for general practitioners (GPs) to help their patients make that switch. Through the use of relatively simple, empowering interventions like education, support, advice and homework assignments, the intervention specifically aims at damming avoiding tendencies and at promoting an active approach of psychosocial difficulties.

Introduction

Common mental disorders (CMDs) are prevalent in general practice; estimates of CMDs in consecutive attendees vary between 20 and 50%, depending on the methods of assessment.[1-3] There is ample evidence that most - if not all - CMDs are stress-related insofar that life events and psychosocial difficulties influence their onset, course and resolution.[3-8] This applies equally to disorders that are diagnosable according to standardised diagnostic criteria (DSM-IV or ICD-10)[9;10] and disorders that are not diagnosable in primary care. Since many of these stress-related disorders are not diagnosable according to standard psychiatric classifications,[11-13] GPs often use ideosyncratic diagnostic labels such as "(chronic) stress", "distress" or "nervous breakdown", or they use "problem-diagnoses" indicating just the social difficulty (e.g. "marital problem" or "overworked"), expressing the stress-relatedness of the disorders they encounter.[14-17] In Dutch general practice the incidence of recorded "nervous breakdown" was found to be 5-14 per 1000 practice population.[14;15] In Australian general practice "stress-related disorders" were diagnosed in 2.6% of consecutive patients, only second in place after mood disorders (4%).[17]

Stress, nervous breakdown and demoralisation

Stress results from an imbalance between demands and perceived abilities to cope with those demands.[18] Demands include such diverse issues as commitments (e.g. work, housekeeping, child care), life events (e.g. marriage, job change, loss of a loved one) and psychosocial difficulties (e.g. financial problems, marital conflict, work overload). Coping, comprising cognitive and behavioural actions used to manage the demands, can be distinguished into two broad categories: approach and avoidance.[19;20] Approach coping, also called problem-focused coping, aims at changing or controlling the demands, whereas avoidant coping, also called emotion-focused coping, aims at reducing the negative affective consequences of the demands. In the face of stress, worry, irritability, feeling tense, disturbed sleep, emotional instability and fatigue are common symptoms of distress. The level of distress actually reflects the amount of mental effort that individuals have to put into coping with their stressors while trying to preserve their habitual level of psychosocial functioning.[21] A failure to cope results in a breakdown of psychosocial functioning, often called a "nervous breakdown" by the lay public.[22;23] Dutch GPs actually use the same label as a proper diagnosis in daily practice.[24] Since formally used diagnostic classification systems lack such a category and there is very little reported research on the actual diagnoses GPs utilise in everyday practice, we are not aware of any diagnostic labels such as "nervous breakdown" being employed by GPs in other countries. A "nervous breakdown" is the breaking point where the individual becomes demoralised, as described by Jerome Frank,[25;26] and gives in. Demoralisation may be viewed as a combination of distress and subjective incompetence, and it is distinguishable from depression by the absence of anhedonia.[27] As opposed to psychiatric illness, demoralisation is considered to be a normal response to adversity.[28] At the heart of demoralisation is a breakdown in coping; the person no longer knows what to do.[29]

Adverse consequences of demoralisation and sick leave

Published evidence suggests that CMDs are a risk factor for sickness absence from work.[30-34] We believe that demoralisation is an important linking pin between CMDs and sick leave, which is often long-lasting. The significance of demoralisation leading to sick leave, has not

been widely recognised.[35;36] However, sick leave for psychosocial reasons can have serious adverse consequences, as we will elaborate below.
The event of giving in comprises an element of avoidant coping - that is, the individual withdraws from the difficult situation in which the struggle to get control over the situation is threatened to be lost.[20] As long as the avoidance provides a temporary solution, to alleviate the pressure and to give the person time to re-appraise the situation and to recuperate from the tension and exhaustion brought on by the distress, there is nothing wrong with avoidance. However, some individuals cling on to the avoidance, as they are not able to think of any other solutions. Persistent distress may give rise to functional somatic complaints and subsequent somatisation.[37] Moreover, some distressed patients go on to develop a true psychiatric disorder, notably major depression or anxiety disorder, based on specific vulnerabilities.[38] Both the persistence of avoidance and the occurrence of somatisation, depression or anxiety can interfere with attempts to restore social functioning and return to work, which may result in long-term sickness absence and even in disability benefit claims. Some older Dutch studies of sick-listed employees with a “nervous breakdown” showed that 1 in every 5 employees stayed on sick leave for more than one year.[39] A more recent study of a similar Dutch cohort of employees revealed that this outcome has not changed: sickness absence exceeded a whole year in 20% of the cases.[40] In The Netherlands the total costs government and employers spend on sickness absence and disability benefits for psychological reasons are estimated to amount up to 8.2 billion Euros annually.[41] About one third of all disability benefits (about 3 billion Euros annually) is being paid on behalf of mental disorders.[42] There are no reasons to believe that mental disorders leading to long-term sickness absence is an exclusive Dutch problem.[43] In Norway sickness absence was attributed to psychological problems in 16% of all cases.[33] In the UK 11% of all sickness absence is attributable to stress.[44] Among London civil servants psychological problems were found to be the second most important cause of long-term sickness absence.[30] Work is a significant contributor to the quality of life. A job structures a person’s life and offers opportunities for self-realisation and satisfaction. Whereas work makes people feel useful and valued, long-term sickness absence and being on disability benefits carry a great risk of social marginalisation.[36]

Recovery from a breakdown

Clinical observation of people recovering from a “nervous breakdown” has shown that the recovery process involves three stages: crisis, problem solving, and restoring social functioning.[45] This three-staged process bears a striking resemblance to the treatment model of stress inoculation training (SIT) with its 3 phases.[46] The first SIT-phase is an educational phase aimed at helping the patient better understand the nature of stress and its effects. The second phase focuses on the acquisition of a repertoire of coping skills, and the third phase involves the application of these skills to increasingly challenging situations.
Stage 1: crisis. Being surprised by a sudden unanticipated breakdown, patients often are more or less “in crisis”.[47] They have dropped major social roles, especially the occupational role. Since they were not able to cope with their difficulties anymore, the patients are extremely distressed and demoralised. They wish be “as far away from it all” as possible. The first step towards recovery involves acceptance of the situation, including the breakdown, as it is, and acknowledgement of the inadequacy of their coping strategies employed so far. The next step involves a reorientation to the problematic situation and to

alternative possibilities to cope with it. Whereas giving in implies loss of control, acceptance, acknowledgement and reorientation imply the beginning of regaining that control. As the patients develop more and more understanding of their situation and how they got there, the demoralisation and distress decrease.

Stage 2: problem solving. Once the patients have a full understanding of their problems, how they were trying to cope with them and why that did not work, they start to consider alternative possibilities for coping with their various problems. Since in many cases multiple problems are implicated, and solving all of them at the same time does not seem feasible, it is helpful to prioritise the problems.[48] It is also helpful to involve significant others in the problem solving process.[47]

Stage 3: restoring social functioning. As more and more problems are successfully solved - or at least made manageable - the patients are able to take up (parts of) the social roles they have dropped earlier. This often involves talking to, or negotiating with, significant others, for instance the manager. Partial return to work appears to facilitate full return to work at a later time.[49]

Although recovery from a “nervous breakdown” seems to be simple and straightforward - and, indeed, many patients manage to recover within an acceptable time span with no more assistance than the help from their family and friends - a substantial minority of patients stay at home and “away from it all” for considerable periods of time, risking social marginalisation. Since avoidant coping is consistently associated with poor mental health outcomes,[19] we presume that whether or not the patient is able to switch from avoidance to “approach coping” early in stage 1 is probably the crucial factor determining the outcome of a “nervous breakdown”.[45]

The role of general practice

Nearly all employees who are on sick leave for psychological reasons consult their GP.[50] Most patients with a “nervous breakdown” are exclusively managed in primary care, and not referred to specialised secondary care.[24] In most cases the GP will have no problem recognising the mental disorder because, in the relation of trust that the patients and doctor are having, the distressed patients will be readily prepared to share their concerns with their doctor. However, the GP does experience problems in discerning diagnosable depressive and anxiety disorders in these patients. One out of five patients diagnosed by their GP as having a “nervous breakdown” has in fact prominent, but unrecognised, symptoms of depression or anxiety, which are associated with poor recovery.[51]

GPs see their “nervous breakdown” patients on average almost three times and they often go along with the patients’ desire to be left alone.[24] GPs advice their “nervous breakdown” patients more often to go or stay on sick leave, to take rest and to seek distraction and relaxation, than to actively approach the difficulties.[24] In this manner, GPs - unintentionally - stimulate passive avoidance in stead of actively coping with the situation, and increase the risk of prolonged disability and ultimate loss of employment.[45] Potentially harmful consequences are loss of daily structure, diminished social contacts and deterioration of self-esteem. The distress of a persisting crisis may, in vulnerable people, even when a diagnosable mental disorder (major depression or anxiety disorder) was not yet present shortly after the breakdown, lead to the development of such a disorder later on. The risk of long-term sickness absence, loss of employment and marginalisation has been mentioned above.

Collaboration between GPs and the occupational health care system seems to be in the best interest of patients with a “nervous breakdown”. However, co-operation is not common practice and poor communication leaves room for improvement.[52] Recently, the Dutch College of General Practitioners and the Netherlands Society of Occupational Medicine issued a guideline for the collaboration of GPs and occupational physicians with respect to the treatment of patients with a “nervous breakdown”.[53]

The Minimal Intervention for Stress-related mental disorders with Sick leave (MISS)
We have outlined an activating intervention for patients with a “nervous breakdown”,[45] which proved to be effective in reducing sick leave by 30% in an occupational health care setting.[54] Taking into account that GPs only have limited time to spend on their patients, we have developed a Minimal Intervention for patients with Stress-related mental disorders who are on Sick leave (MISS) in general practice. The leading question was: if GPs have no more than three consultations available for each “nervous breakdown” patient, then what should they do in these three consultations? We judged that the GPs should focus primarily on the first stage of the recovery process, especially on the switch the patients have to make from passive avoidance to active “approach coping”. The GPs should try to put their patients on the right track to recovery as soon as possible, using a minimal amount of time, effort and skills. The MISS consists basically of 5 elements: assessment, education, advice, monitoring, and referral (if necessary).

Assessment implies first of all detecting mental disorders and having patients acknowledge their distress. Moreover, the GP should detect diagnosable depressive and anxiety disorders and, when present, deal with these disorders separately.[47] The Four-Dimensional Symptom Questionnaire (4DSQ) is used to quantify the level of distress, and to detect depression, anxiety, and somatization.[55] Guidelines from the Dutch College of General Practitioners are available to support the diagnosis and treatment of diagnosable depressive and anxiety disorders.[56;57] During the first consultation, often a provisional diagnosis is made, especially when physical illness has not yet been ruled out. Between the first and second consultation, which are scheduled one week apart, the patient fills in the 4DSQ and may have some somatic diagnostic examinations performed. Usually, it is possible to make a definite diagnosis during the second consultation.
Education aims, in line with the SIT-model,[46] at promoting the patients’ understanding and acceptance of the origin and cause of the breakdown. Furthermore, information is given on the recovery process of a “nervous breakdown”, and the patients’ active role in this process is emphasised. “Nervous breakdown” is explained as a natural response to overwhelming stress.[28] Evoking positive and realistic expectations by providing an acceptable rationale is a powerful intervention.[47;58] An information leaflet, which also contains advice and tips on how to deal with the breakdown (see below), is available for the patient to read at home and discuss with family and friends. When the suspicion of a stress-related mental disorder is relatively high, although the diagnosis may not yet be definite, the education is already provided in the first consultation in order not to lose precious time. The GP also provides information about the role and function of the occupational physician in the Netherlands.
Advice is giving in the first two consultations about coping with the breakdown, making a start with solving the problems, and planning to take up social functioning gradually. In analogy with the dual process of coping with bereavement,[59] the GP explains that it is important not

only to take rest and to relax, but also to alternate this avoiding of the problems with actively approaching them. One of the first "approaching" activities is writing down the troubling things the patient tends to be brooding about all the time.[60] These so-called "worry sessions", one or two times a day for 30-45 minutes, promote coming to grips with the difficulties and exploring potential solutions.[47;61;62] The patients are also advised to schedule necessary activities of daily living, such as child care and housekeeping, and to think about ways to partially return to work even when not all problems have been solved. The patients are advised to adhere to a daily schedule in which the activities mentioned above find a place. Finally, the patients are advised to see their occupational physician at an early stage, to help solve problems in the workplace when necessary, and to help prepare gradual work resumption when possible.

Monitoring is about ensuring the patient is getting on the right track towards recovery. The right track implies a focus on problems (and possible solutions) instead of a focus on symptoms. The patients have to investigate their problems and consider alternative ways of coping.[47] The switch in the patients' focus has often already occurred before the second consultation, but it should in any case have occurred after four weeks, when the third consultation is scheduled.

Referral is indicated if the necessary switch - i.e. the switch from symptoms to problems, from avoidance to approach of the difficulties - has not occurred, and the patients are still in crisis after 4 weeks of sick leave. The GP should realise that the patients at that point are at risk for prolonged sick leave and loss of employment in the long run. As the patients are not likely to benefit from more time off, a more specialised treatment is warranted. The GP may refer the patients to a counsellor, social worker or a (cognitive behavioural) psychotherapist, preferably after consulting with the occupational physician.

In order to learn to use the MISS intervention, we have developed an 11-hours training course comprising 4 sessions in 2.5 months time.

Discussion

We have asked attention for the problems of stress and coping in relation to common mental disorders in general practice patients. More specifically, we have described demoralisation and "nervous breakdown" as hazardous consequences of a failure to cope with the demands in a person's life. We do not conceptualise demoralisation/"nervous breakdown" as a distinct diagnostic category that should be included in existing diagnostic classification systems (such as the DSM-IV) next to depressive and anxiety disorders. Rather, we look upon demoralisation/"nervous breakdown" as an important dimension of mental disorders that cuts across all established diagnostic categories. In addition, demoralisation/"nervous breakdown" may be the most important mental problem in cases where no formal psychiatric disorders are diagnosable. We feel that it is important for GPs to pay attention to the patients' stress in their lives, how they (are trying to) cope with that, and what the consequences are, and not to concentrate too much (and certainly not exclusively) on whether the patients fulfil the requirements of a formal mental disorder diagnosis.

Furthermore, we have described the risks involved in long-standing sick leave when patients continue not coping, and presented the Minimal Intervention for patients with Stress-related mental disorders who have gone on Sick leave (MISS) to activate the patients to more active coping strategies. Through the use of relatively simple, empowering interventions like education, support, advice and homework assignments, the intervention specifically aims at

damming avoiding tendencies and at promoting an active approach of psychosocial problems. The ultimate goal is to prevent long-term sickness absence, loss of employment and social marginalisation. We have argued that GPs should focus on the first crisis-like stage of the breakdown, helping their patients to regain control and start coping again. We have recently completed a randomised controlled trial to evaluate the effectiveness of teaching GPs to deliver the MISS,[63] and demonstrated a significant reduction of sick leave in patients identified by their GP as having stress-related mental disorders (hazard ratio for return to work: 1.72, $p = 0.005$).[64]

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3

Effectiveness of a Minimal Intervention for Stress-related mental disorders with Sick leave (MISS); study protocol of a cluster randomised controlled trial in general practice [ISRCTN43779641]

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Abstract

Background. The main aims of this paper are to describe the setting and design of a Minimal Intervention in general practice for Stress-related mental disorders in patients on Sick leave (MISS), as well as to ascertain the study complies with the requirements for a cluster randomised controlled trial (RCT). The potential adverse consequences of sick leave due to Stress-related Mental Disorders (SMDs) are extensive, but often not recognised. Since most people having SMDs with sick leave consult their general practitioner (GP) at an early stage, a tailored intervention given by GPs is justified. We provide a detailed description of the MISS; that is more accurate assessment, education, advice and monitoring to treat SMDs in patients on sick leave. Our hypothesis is that the MISS will be more effective compared to the usual care, in reducing days of sick leave of these patients.

Methods. The design is a pragmatic RCT. Randomisation is at the level of GPs. They received the MISS-training versus no training, in order to compare the MISS vs. usual care at patient level. Enrolment of patients took place after screening in the source population, that comprised 20-60 year old primary care attendees. Inclusion criteria were: moderately elevated distress levels, having a paid job and sick leave for no longer than three months. There is a one year follow up. The primary outcome measure is lasting full return to work. Reduction of SMD- symptoms is one of the secondary outcome measures. Forty-six GPs and 433 patients agreed to participate.

Discussion. In our study design, attention is given to the practical application of the requirements for a pragmatic trial. The results of this cluster RCT will add to the evidence about treatment options in general practice for SMDs in patients on sick leave, and might contribute to a new and appropriate guideline. These results will be available at the end of 2006.

Background

Stress-related mental disorders (SMDs)

Stress results from an imbalance between demands and resources[1]. It is a psychological, physiological and behavioural response by individuals when they perceive a lack of equilibrium between the demands placed upon them and their ability to meet those demands. This response, over a period of time, leads to ill-health[2] and it is important to respect the roles of personal, social, economic, occupational and physical health problems in determining and shaping this psychological disability[3]. Fatigue, tenseness, irritability, apathy, sleeping disorder, emotional instability, rumination and concentration- problems are examples of common symptoms related to stress and a failure to cope with demands while resources (i.e. the abilities to meet those demands) are not sufficient. In addition, some patients with persistent distress go on to develop a psychiatric disorder, notably major depression or anxiety disorder, based on specific vulnerabilities. Plus, persistent distress may give rise to somatic complaints and subsequent somatization[4]. It is clear and evidence-based to treat major psychiatric disorders with medication or counselling, whereas evidence-based interventions for the whole range of Stress-related Mental Disorders (SMDs) are still under development.

SMDs and sick leave

The societal and financial costs of dysfunction in terms of (long term) sick leave due to SMDs are extensive. In the Netherlands, almost one million workers are entitled to disability benefits (9 percent of the working population), this prevalence is high compared with other countries[5]. About one third of the 9.407 billion Euros in 2004 of the disability benefits in the Netherlands was paid to persons with mental health problems[6]. Whereas only ten percent of those receiving disability benefits have an actual psychiatric disorder, ninety percent is due to what patients and care-providers consider to be SMDs[7]. Furthermore, the composition of the group of workers who receive disability benefit in the Netherlands is changing disquietingly: currently young female employees, mostly with mental health problems, constitute the majority of new cases[8]. Chronicity of SMDs with sick leave is growing, although several studies indicate that SMDs can be treated successfully if they are diagnosed and treated at an early stage[9]. However, for a long time the usual approach to SMDs with sick leave was the reverse: advice to take rest and not return to work before all complaints had disappeared. Last but not least, patients with SMDs being on sick leave definitely cannot be reduced to only an economic problem; of course much personal suffering is involved. Moreover, the value of work is undisputed and in cases of (prolonged) sick leave there is a risk of permanent loss of employment.

General Practice treatment of SMDs in patients on sick leave

Nearly every employee contacts the GP at the beginning of the sick leave. Most patients having SMDs are managed in primary care, and not referred to specialised secondary care. And despite the fact that mental health problems are common in primary care, GP's may still find it difficult to diagnose and treat them, unless they have a high index of suspicion[10]. Due to the collaborative nature of the doctor-patient relationship in general practice, many GPs may be overly cautious to attribute symptoms to a psychosocial cause. Another issue is an adequate differential diagnosis; many patients in primary care have symptoms related to anxiety, depression, somatization, or all three. In one out of five patients having a SMD there

are prominent, although unrecognised symptoms of depression or anxiety, which are associated with a poor prognosis. A further pitfall is that GPs often tend to go along with the patient's request for rest and being left alone. Often GPs advise to go or stay on sick leave, to take rest, seek distraction and relaxation, instead of actively confront and cope with the difficulties. The distress of a lasting crisis combined with existing vulnerabilities may lead to prolonged disability and contribute to the development of serious mental disorders, e.g. depression or anxiety disorders. Earlier research revealed that about 20% of patients having a SMD stayed on sick leave for more than a whole year[11]. Cooperation between GPs and the occupational health care system seems to be in the best interest of all involved and also the preferred way to manage SMDs with sick leave.

The Minimal Intervention for Stress-related mental disorders with Sick leave (MISS)
Terluin and Van der Klink[12] have outlined an activating intervention for patients having a SMD with sick leave, that already proved to be effective in reducing sick leave by 30% in an occupational health care setting[13]. Taken into account that GPs only have limited time during consulting hours, we developed the Minimal Intervention for Stress-related mental disorders with Sick leave (MISS) for general practice. In the MISS the principle of time contingency is used. Also, parts of more specialised psychological treatments like Cognitive Behavioural Therapy (CBT[14]) and Problem Solving Treatment (PST[15;16]) are incorporated. With respect to the role of gatekeeper in primary care practice, only basic principles of CBT and PST were considered relevant for GPs[17].
The MISS is a prototypical intervention for SMDs with sick leave in general practices, aiming specifically at successful rehabilitation and preventing long-lasting sick leave. By using specific communication and the minimal amount of time necessary, the GP helps the patient on the accurate and time-contingent course. The MISS should take no more than 3 consultations of 10-20 minutes, and consists basically of 5 elements: assessment, education, advice, monitoring and, if necessary, referral.
Assessment implies in the first place to identify patients having a SMD and help them to acknowledge their distress. Second, the GP detects significant depression and anxiety, and propose management steps for these problems separately. The Four-Dimensional Symptom Questionnaire (4DSQ[18]) is used in the MISS to quantify the level of distress, and to detect symptoms of depression and anxiety. Guidelines from the Dutch College of General Practitioners are available to support the diagnosis and treatment of possible depression and anxiety disorders[19;20]. When physical illness has not yet been ruled out, the patient may have some somatic diagnostic examinations done, next to filling in the 4DSQ.
Education aims at promoting the patient's understanding and acceptance of the cause of the breakdown. Information is given on the normal course after having a SMD with sick leave, in this the patient's own active role is emphasised. The GP also gives information about the role and function of the occupational physician in the health care system. When the diagnosis may not yet be definitive, although the suspicion of a SMD is present, the education is still provided in the first consultation in order not to lose precious time.
Advice is given on coping with the breakdown, making a start with solving the problems, and planning to gradually take up social functioning. The GP underlines the importance of a balance in taking rest and making an active approach towards the problems, like using a rumination session (that is writing down what specifically troubles the patient) one or two times a day for 30-45 minutes. The patient is also advised to schedule necessary activities of

daily living, such as children's care and housekeeping. Furthermore the patient is recommended to visit his or her occupational physician without delay, and to explore ways after which it is possible to partially return to work, even when not all symptoms have disappeared.
Monitoring is about ensuring the patient is moving towards the accurate course. This implies a focus on the problems (and possible solutions) in stead of symptoms. The patient has to investigate the specific problems and consider different ways to cope. The switch in the patient's focus has often already occurred before the second consultation; however it should in any case have occurred after four weeks of sick leave.
Referral to specialised care comes into play when there is no evidence of progression after four weeks of sick leave. The GP should realize that the patient is at risk for prolonged sick leave and ultimately loss of employment. A more specialised treatment is necessary since the patient is not likely to benefit from more time off. The GP may refer the patient to a counsellor, social worker or a (cognitive behavioural) psychotherapist, ideally after consulting with the occupational physician.

Methods

Objective

The central aim of this pragmatic cluster randomised controlled trial (RCT) is to investigate the effectiveness of the MISS in general practice. Our hypothesis is that GPs who carry out the MISS will be more effective than GPs who perform usual care in reducing the number of days of sick leave, as well as in reducing symptoms of SMDs in patients. Usual care in general practice contains the guidelines on depression[21] and anxiety[22]. In the case of the MISS, GPs are trained in topic- specific knowledge on patients with SMDs on sick leave. Because GPs, who have learned to apply the MISS, cannot be expected to perform this intervention in some patients and treat others as they used to do prior to the training, randomisation at the level of individual patients was not feasible. To avoid possible contamination between the conditions, a cluster design randomising at the level of GPs was chosen. There will be a one year follow up on the patients to assess the outcome measures and factors involved in the process of sick leave and return to work. The study design, protocol and procedures were approved by the Medical Ethics Committee of the VU University Medical Centre.

Participants

GPs. The recruitment of GPs was split up in four different rounds. We approached GPs in two different districts where the Department of General Practice of the VU University Medical Centre has some type of network positioned. A total of 46 GPs signed informed consent.
Patients. In order to recruit enough eligible patients, we made use of the computerised patient record system and approached the source population of patients (n= 22.740) by mail. The source population consisted of all primary care attendees (20-60 years) who visited consulting hours of the participating GPs. GP's excluded only patients with very severe psychiatric disorders (mania or psychosis), patients with terminal illness or an inadequate command of the Dutch language. The source population of attendees was asked only to respond when they met our criteria: moderately elevated distress level (measured with 3 questions of the 4DSQ distress scale[23]), having paid work and being (partially) on sick leave for no longer than three months (see table 1).

Every one or two weeks we approached the source population, until enrolment of a sufficient number of patients from a particular GP was realised. Final recruitment took place by phone survey of the patients who returned the questionnaire and met the criteria. A total of 433 patients (1,9%) who could and also wanted to participate were enrolled (see figure). The overall response percentage on our screening method was 51.5%, this was measured in a group of 336 randomly selected attendees. This labour-intensive however highly successful method of screening ensures that we recruited patients having SMDs with sick leave in stead of patients who actually get an intervention for their complaints.

Table 1. Eligibility criteria

	No	Sometimes	Regularly or often
1. During the past week, did you suffer from worry?*	0	1	2
2. During the past week, did you suffer from listlessness?*	0	1	2
3. During the past week, did you feel tense?*	0	1	2
4. Total score 4 or higher?	Yes		No
5. Do you currently have a paid job?	Yes		No
6. Have you been on sick leave, now for a maximum period of three months?	Yes		No

Patients were asked to only return the questionnaire if they answered 'yes' to items 4,5 and 6 and were willing to participate.

*Four-Dimensional Symptoms Questionnaire Distress scale, (4DSQ, [23])

Intervention at the level of general practitioners

In order to use the intervention, additional training in the MISS was given to intervention GPs by one of the authors (BT), and an occupational physician. This training existed of two times 3,5 hours and 2 times follow-up of 2 hours (total of 11 hours). Skills needed for successful treatment were accentuated. The participating GPs own experiences were evaluated; they were expected to provide case histories and to practice with the different parts of the intervention during the training. Screening of eligible patients started after the MISS group got the second training. When a patient had signed the informed consent (about four weeks after oral informed consent in the telephonic baseline measure), the GP was informed of the participation. Actual application of the elements of the MISS and steps in usual care are measured with a questionnaire.

Intervention at the level of the patients

During the baseline interview all patients were asked whether they had planned another visit to their GP. If not they were advised to consider this, in order to give the GPs the opportunity to start with an intervention. Even though, it should be noted that neither the GPs were obliged to apply the MISS or any other intervention for mental disorders, nor were the patients obliged to go visit their GPs. No intervention was done on the actual completion or successfulness of the application of the MISS, the present method comprises real clinical practice in primary care.

Outcome measures

Sick leave. The primary outcome measure is defined as: duration of sick leave in calendar days from the first day of sick leave to full return to work, lasting at least 4 weeks without

(partial or full) relapse. Variables of the rehabilitation process itself, like the time to first (partial or full) return to work, total days of sick leave in the whole year, and (partial or full) return to work rates after 2, 6 and 12 months, are secondary outcome measures. Sick leave in the past year is considered to be a prognostic factor for our primary outcome measure, as are job content data[24;25].

Table 2. Outcome measures

		Baseline	Follow up in months		
Outcome measure	**Instrument**	**0**	**2**	**6**	**12**
Primary outcome (dependent)					
Lasting return to work: duration of sick leave in calendar days from the first day of sick leave to full return to work, for at least 4 weeks without (partial or full) relapse	Patients report	X	X	X	X
Secondary outcomes (dependent)					
Time to first (full or partial) return to work	Patients report	X	X	X	X
Return to work rates	Patients report	X	X	X	X
Total days of sick leave during one year follow up	Patients report	X	X	X	X
Recurrence of sick leave	Patients report	X	X	X	X
Reduction of symptoms	4DSQ [36;40]	X	X	X	X
Health state profile	Euroqol [33]	X	X	X	X
Costs of health care and loss of productivity	Tic-P [30]	X	X	X	X
Absenteeism, quality and quantity of work	HPQ [41;42]	X		X	
Problem evaluation	Psychlops (MYMOP) [43;44]	X	X	X	X
Coping processes	Ways of Coping Questionnaire [29]	X	X	X	X
Patient satisfaction	Patients report		X	X	X
Application of the MISS: number of visits, diagnosis, advice & treatment, proceeding of recovery process over the past year	Medical record & questionnaire filled in by GP				X
Prognostic measures (independent predictor or covariate)					
Mental disorders	PRIME-MD [45;46]	X			
Sick leave in year before	Patients report	X			
Problems, life events, chronic illnesses	Patients report	X		X	X
Work experience / burn out	UBOS [24]	X			X
Job content data, job stress	JCQ [25]	X			
Critical incidents	HPQ [47]	X		X	
Neuroticism	NEO-FFI [27]	X			

Reduction of SMD symptoms. An important secondary outcome measure is reduction in symptoms of depression, anxiety, somatization and distress, measured with the 4DSQ[26]. Life-events and problems, chronic illnesses and neuroticism[27] are prognostic measures for this outcome. Problem evaluation[28] and coping styles[29] are measured to evaluate the effective components of the MISS: problem- and solution focus skills of patients.
Economic evaluation. Cost effectiveness will be evaluated from societal perspective (that is, irrespective of who is paying for the costs to gain an effect) by using the Tic-P[30]. The employers perspective (expenditures for the employer) is represented by the HPQ[31;32]. The EuroQol[33] measures general health state, and as a result quality of life status, that can be compared with a wide range of conditions in health care.

Data collection

At baseline, patients who entered the study were measured by a phone survey and received a questionnaire by mail. Follow-up measurements, again a phone survey followed by a questionnaire, were scheduled at 2, 6 and 12 months after baseline. All outcomes were

measured at the level of the patient, except for the GP interventions and skills. These were reported by the GPs two months after baseline. Moreover, data on received health care were extracted from the medical records after the completion of the one year follow-up.

Power & sample size

Proportions used to determine the sample size needed, were adopted from a related study completed in the occupational health care setting[34]. In that study, after a period of 3 months 79% in the intervention group versus 64% in the control group had fully returned to work. In order to detect a relevant difference in survival analysis on our primary outcome measure, nQuery Advisor [35] was used to calculate the sample size. With a power of 80% at a 0.05 level two-sided log-rank test for equality of survival curves between the MISS group proportion still on sick leave of 0.21 and a usual care group proportion of 0.36 at the given time of 3 months, the sample size needed in each group was 126 (with a constant hazard ratio of 1.528). Taking into account an intracluster correlation coefficient (ICC) of .025 (clustering effect in our groups is not presumed to be large) for randomisation at GP level and 7 patients per cluster (GP), a total of 290 patients are needed. Assuming a dropout rate of 30% (approximately 10% at each follow up), inclusion of a total of 415 patients is necessary.

Randomisation

Randomisation took place at the level of GPs, after each of the four recruitment moments and after the GPs signed informed consent. Because balance between groups in size and characteristics was presumed all four times GPs were randomised, no blocking or stratification was used. We developed the following procedure to conceal allocation. The names of the GP's (and dummy in an uneven group) were put on a list of which the order was subsequently randomised by one person (IMB). Another person (BT) independently drew up a randomised list of codes (1 = MISS group and 2 = control group) with an equal number of '1' and '2' codes up to the number of GPs being randomised. Finally, these two lists were brought together and the first GP on the list was allocated to the group indicated by the first code; and so on. As a result, 24 GPs were allocated to the intervention (MISS) group and 22 GPs were allocated to the control (usual care) group.

Implementation

After assigning the GPs and training was given to the MISS group, patients were enrolled by screening the source population (see participants). The general practice team gave entrance to data on the source population, the source population was given the inclusion criteria through a screening questionnaire. The research assistance team was responsible for the final recruitment. They gave information in a phone survey and asked the patient informed consent to participate.

Blinding

Patients were kept unaware that two different interventions were studied; both groups were given exactly the same information and questionnaires. The patients, as well as the external interviewers who carried out the phone surveys, were told that the study was about stress and sick leave. Finally, the internal research assistance team responsible for the process of data collection knew that the study involved a training of half of the GPs; nevertheless the internal research team had no information on which GPs were allocated to what conditions.

Statistical methods

First of all, baseline similarity between the MISS and usual care groups will be examined, and baseline characteristics of drop outs and completers will be compared. Cox regression analyses will be used to investigate the intervention effect, by analysing differences in outcome with survival analysis of the primary outcome measure between the MISS and usual care group. To correct for misclassification of patients and severity of complaints (inclusion is only by level of distress with sick leave), and as a consequence to avoid bias in the effect, baseline measures of psychological symptoms (by means of the 4DSQ [36] & PRIME-MD [37]), as well as medical records will be examined. Additionally, subgroup analysis can be done by level of severity of complaints.

Linear and logistic multilevel analyses will be used to investigate the intervention effect on all secondary outcome measures: rates of return to work, psychological symptoms, problem experience and coping style. Also, longitudinal multivariate analysis will be used to examine differences in improvement in all secondary outcome measures between the treatment groups. Analysis will be performed on an intention-to-treat basis and intra-class-correlation will be calculated to correct for possible clustering of observations. Levels included will be: repeated measures, patients and GPs. Subgroups for analysis will be modelled by the prognostic factors mentioned.

Costs will be measured and valued from a societal perspective. Mean direct and indirect medical costs (measured with the Tic-P[30]), costs of productivity loss due to sick leave (measured with the WHO HPQ[38]) and total costs will be compared between both groups. Confidence intervals around mean differences will be estimated with bootstrapping methods. With regard tot the primary outcome, sick leave, a cost benefit analysis will be performed, in which costs of productivity loss due to sick leave will be compared with direct en indirect medical costs.

A cost-effectiveness analysis will be performed to assess the incremental costs per unit improvement on the 4DSQ [39]. Bootstrapping methods will be used to estimate the confidence interval for the cost-effectiveness ratio and to a draw cost-effectiveness plane. Similarly, utility assessed with the EuroQol [33] will be used to estimates the incremental costs per Qualy gained in a cost-utility analysis.

As regards the prognostic measures, univariate analyses will be used to select relevant factors, with a focus on identifying prognostic factors for our primary outcome measure. Subsequently, Cox regression analyses and logistic regression analysis will be performed on these relevant factors.

Discussion

SMDs in primary care

This project is developed for the primary care setting with its' typical case load of stress-related mental disorders, and not for specialised care in which patients have more clearly defined mental disorders. We provide an intervention that is aimed at better recognition, good communication, and a time-contingent framed recovery process. Our approach of SMDs, with the need to identify specific psychiatric disorders where they exist and also to respect the roles of daily life in determining and shaping psychological disability, is an example of specified stepped care in general practice. Potential risk factors for chronicity are

pointed out in our training, and early recognition and treatment is the main goal of the MISS. The role of more specialised care is well acknowledged in the intervention.

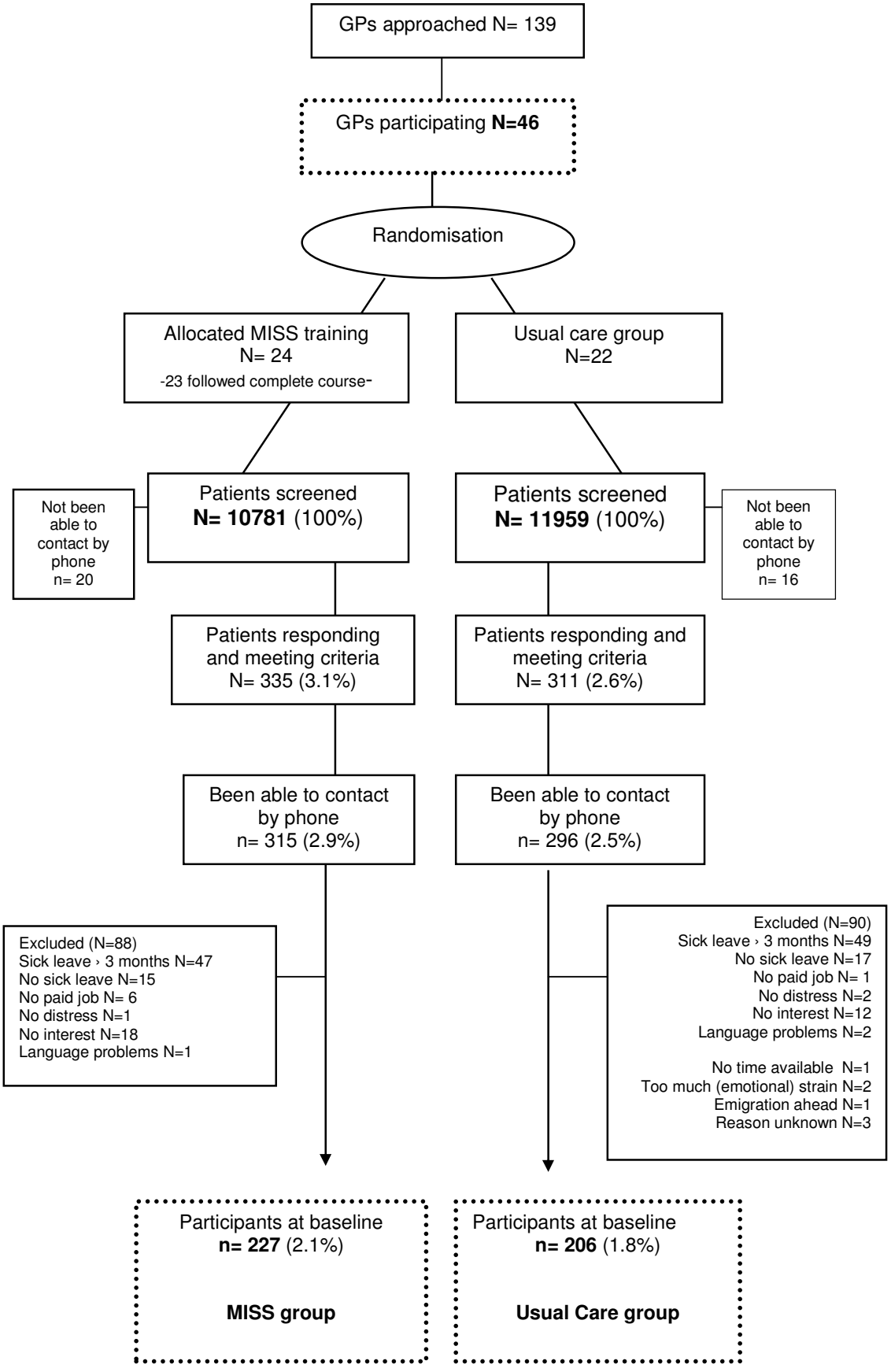
Benefits of our screening method

Particular strength of our study protocol is the method of recruiting patients. By using the computerised patient record system, we screened the whole population of general practice attendees and thereby determined who entered the study, instead of chartering the GPs to select their patients. Therefore, similarity in both groups is assured and we avoided selection bias. Also, we did not have difficulties in including enough eligible patients, which is often a problem in primary care trials. Furthermore, the current method allows us to consider the pragmatic effectiveness and to avoid interference with daily practice of consulting hours. In this trial, follow-up is on patients having SMDs with sick leave, instead of patients who actually get an intervention for their complaints. Good external validity (i.e. generalizability) is accomplished by this rather heterogeneous, and therefore highly representative, group of patients with SMDs on sick leave. To assure as much internal validity as possible in this pragmatic trial, we randomised on the level of GPs to avoid contamination. In addition, research assistants who collected the data and also the patients were blinded.

Prospect on outcomes

Notably, effectiveness instead of efficacy is studied. We are evaluating what is possible in real clinical practice, rather than under ideal circumstances. As a consequence, mental health state will vary between the participants. Through subgroup analysis on severity of complaints and levels of distress (measured with the PRIME-MD and 4DSQ), we can classify possible high or low risk groups for prolonged disability within this heterogeneous group. Identification of a high risk group for non-recovery may lead to better suited guidelines on stepped care and treatment. We cannot assure that everyone in the MISS group has received the intervention; the GPs were given total freedom in actually delivering the MISS. Nevertheless, the number of visits, diagnoses, recommendations, treatments and proceedings will give us information about the compliance of the GPs and their influence on the effect of the MISS. In this way, daily practice is measured in stead of ideal circumstances. To avoid social desirable answers from the GPs on their advises and treatments, we will also check the medical records of the patients.

Finally, many requirements for a high quality trial are being met. Results of this cluster RCT will contribute to treatment options for patients having SMDs with sick leave in general practice, and might contribute to new and better suited guidelines and stepped care. Results will be available in the end of 2006.


GPs approached N= 139
GPs participating **N=46**
Randomisation
Allocated MISS training
N= 24
-23 followed complete course-
Usual care group
N=22
Not been able to contact by phone n= 20
Patients screened **N= 10781** (100%)
Patients screened **N= 11959** (100%)
Not been able to contact by phone n= 16
Patients responding and meeting criteria N= 335 (3.1%)
Patients responding and meeting criteria N= 311 (2.6%)
Been able to contact by phone n= 315 (2.9%)
Been able to contact by phone n= 296 (2.5%)
Excluded (N=88)
Sick leave › 3 months N=47
No sick leave N=15
No paid job N= 6
No distress N=1
No interest N=18
Language problems N=1
Excluded (N=90)
Sick leave › 3 months N=49
No sick leave N=17
No paid job N= 1
No distress N=2
No interest N=12
Language problems N=2
No time available N=1
Too much (emotional) strain N=2
Emigration ahead N=1
Reason unknown N=3
Participants at baseline **n= 227** (2.1%)
MISS group
Participants at baseline **n= 206** (1.8%)
Usual Care group

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4

A cluster-randomised trial evaluating an intervention for patients with stress-related mental disorders and sick leave in primary care

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Abstract

Objectives: Mental health problems often affect functioning to such an extent that they result in sick leave. The worldwide reported prevalence of mental health problems in the working population is 10%–18%. In developed countries, mental health problems are one of the main grounds for receiving disability benefits. In up to 90% of cases the cause is stress-related, and health-care utilisation is mainly restricted to primary care. The aim of this study was to assess the effectiveness of our Minimal Intervention for Stress-related mental disorders with Sick leave (MISS) in primary care, which is intended to reduce sick leave and prevent chronicity of symptoms.

Design: Cluster-randomised controlled educational trial.

Setting: Primary health-care practices in the Amsterdam area, The Netherlands.

Participants: A total of 433 patients (MISS n = 227, usual care [UC] n = 206) with sick leave and self-reported elevated level of distress.

Interventions: Forty-six primary care physicians were randomised to either receive training in the MISS or to provide UC. Eligible patients were screened by mail.

Outcome measures: The primary outcome measure was duration of sick leave until lasting full return to work. The secondary outcomes were levels of self-reported distress, depression, anxiety, and somatisation.

Results: No superior effect of the MISS was found on duration of sick leave (hazard ratio 1.06, 95% confidence interval 0.87–1.29) nor on severity of self-reported symptoms.

Conclusions: We found no evidence that the MISS is more effective than UC in our study sample of distressed patients. Continuing research should focus on the potential beneficial effects of the MISS; we need to investigate which elements of the intervention might be useful and which elements should be adjusted to make the MISS effective.

Introduction

Mental health problems often affect functioning to such an extent that they result in sick leave [1]. The worldwide reported prevalence in the working population is 10%–18% [2,3]. These problems cause a public health burden resulting in enormous personal and financial costs [4–7]. Sick leave often lasts for a long period of time, and in developed countries, mental health problems are one of the main grounds for receiving disability benefits [8,9]. In up to 90% of mental health problems the cause is stress-related [4–6,10] and health-care utilisation is mainly restricted to primary care [9].

Common psychopathology, as seen in primary care, often starts with failure to cope with personal, social, or occupational demands. The ability to cope or readjust is overtaxed, and this increases the probability that psychological distress will follow [11–13]. Sick leave indicates a process of depleting psychological resources; the patient has stopped trying to cope, and gives in. When not due to more severe psychiatric conditions such as depressive disorder or anxiety disorder, this condition is known as adjustment disorder (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) [14,15], neurasthenia (International Classification of Diseases, tenth revision) [16], or nervous breakdown. Because such patients are labelled with a number of inter-related terms and definitions, we use the term stress-related mental disorder (SMD) to indicate relevant dimensions of psychopathology that are subacute, but not yet chronic, and clearly related to stress. Subsequently to SMDs, persistent distress contributes to more severe psychopathology and chronic conditions such as depression and anxiety disorders [17].

As yet, there are no evidence-based primary care interventions to improve functioning and to prevent long-term sick leave in patients with SMDs. Primary care physicians (PCPs) are not always aware of the potentially harmful consequences of sick leave and stress, because the symptoms seem to be self-limiting. Or, PCPs may be overly cautious and not question the continuation of sick leave nor ask the patient to make more effort to cope with the situation, feeling that this type of response undermines the mutual trust between patient and doctor [18,19].

Methods

The present study is a cluster-randomised controlled effectiveness trial in which PCPs were randomised to an intervention group that was trained to deliver a minimal intervention for stress-related mental disorders, or to a control group that delivered care as usual. Distressed patients on sick leave visiting the practices of both PCP groups were screened, included, and followed up for one year [20]. The Medical Ethics Committee of the VU University Medical Center approved the study protocol and procedures.

Participants

We approached 139 PCPs in two districts where the Department of General Practice of the VU University Medical Center has some type of network positioned. A total of 46 PCPs signed informed consent, both for participating in our trial and for being randomised to either the intervention training or to the usual care (UC) group.

In order to recruit enough eligible patients, we made use of the computerised patient record system and approached the source population of patients (n = 22,740, see Figure 1) by mail.

Figure 1. Patient screener

	No	Sometimes	Regularly or often
1. During the past week, did you suffer from worry?*	0	1	2
2. During the past week, did you suffer from listlessness?*	0	1	2
3. During the past week, did you feel tense?*	0	1	2
4. Total score 4 or higher?	Yes		No
5. Do you currently have a paid job?	Yes		No
6. Have you been on sick leave, now for a maximum period of three months?	Yes		No

Patients were asked to only return the questionnaire if they answered 'yes' to items 4,5 and 6 and were willing to participate.

*Four-Dimensional Symptoms Questionnaire Distress scale, (4DSQ, [23])

The source population consisted of all primary care attenders (20–60 y) who visited consulting hours of the participating PCPs. PCPs excluded only patients with very severe psychiatric disorders (mania or psychosis), patients with terminal illness, or patients with an inadequate command of the Dutch language. The source population of attenders was asked to respond only if they met our criteria. Patient inclusion criteria were symptoms of SMD, and sick leave for no longer than three months from a paid job. Symptoms of SMD were measured by means of self-reported levels of distress (e.g., worrying, listlessness, feeling tense—see Figure 1) in order to recruit patients. We approached the source population every one or two weeks, until a sufficient number of patients from a particular PCP were enrolled. Final recruitment took place by phone survey. All patients who had returned the questionnaire and screened positive on distress and sick leave were contacted. Next, the inclusion criteria on distress and sick leave for no longer than three months were checked again. Since there are no diagnostic criteria, we did not attempt to make a diagnosis of SMD. If positive, patients were asked for their informed consent to be included in the study and to have their data collected and analysed. If the patient consented, the telephonic baseline interview was started. This method of recruitment, unaffected by the PCPs' diagnostic or therapeutic behaviour, ensured that the recruited patients included in the intervention and control groups were comparable, and at least not subjected to selection bias.

Interventions

Over a period of 6–10 wk, the PCPs randomised into the intervention group received training in the Minimal Intervention for Stress-related mental disorders with Sick leave (MISS). The training comprised two sessions of 3.5 h and two regular follow-up sessions of 2 h (total 11 h). The tutors during the training were the PCP who developed the intervention (BT) and an occupational physician. During the training, the PCPs were instructed to use specific methods of communication to help the patient, within three consultations on a time-contingent course, to achieve functional recovery. The MISS takes into account the time constraints under which a PCP works, as well as the position of a PCP as a generalist who does not have the capacity to apply highly specialised interventions. The necessary set of skills was clearly defined and taught to the PCPs. First, the PCPs were taught to diagnose an SMD, and to detect symptoms of depression and anxiety. They were then taught how to give information and promote the patient's understanding and how to emphasise the importance of the patient's active role with regard to successful return to work. Subsequently, they

practised giving advice on the content of functional rehabilitation. Furthermore, the PCPs were taught active monitoring to evaluate whether the patient had made efforts to translate the (work) situation into a problem that could be solved. Lastly, the PCPs were instructed to consider referral to more specialised care in case no progress had been made, since the patient was not likely to benefit from more time off work. The PCPs in the UC group received no information or advice about the content of the intervention beforehand, but were offered the training at the end of the trial. Guidelines for PCPs are available for the treatment of depression [21] and anxiety [22], but not yet specifically for SMDs.
Actual treatment of the participating patients was left to the discretion of the PCPs, who were informed of a patient's participation only after a month. At baseline, patients were asked whether or not they had planned another visit to their PCP. If not, they were asked if they were considering another visit. The PCP was not obliged to apply the MISS or any other intervention, nor were the patients obliged to visit their PCP.

Objectives
The aim of this study was to assess the effectiveness of our MISS in primary care, which is intended to reduce sick leave and prevent chronicity of SMD symptoms in patients. We hypothesised that the MISS would be more effective than UC, particularly in patients who had been diagnosed with SMD by the PCP.

Outcomes
The primary outcome was duration of sick leave in calendar days from the first day of sick leave until full (not part-time) return to work, lasting for a period of at least 4 wk without partial or full relapse into sick leave. Patients were asked to record their days of sick leave, and this information was collected at baseline and after 2, 6, and 12 mo during telephone interviews. The secondary outcome measures were self-reported symptoms of distress, depression, anxiety, and somatisation. These were measured with the Four-Dimensional Symptom Questionnaire (4DSQ [23]) at baseline and at 2, 6, and 12 mo by mailed questionnaires. Elevated depression, anxiety, and somatisation scores are indicative of the existence of a depressive, anxiety, or somatisation disorder, whereas, in the absence of elevated depression, anxiety, and somatisation scores, an elevated distress score is indicative of an SMD. Two months after the baseline assessment, the PCPs in both groups were asked to fill in a structured questionnaire on the care provided and any diagnoses or working hypotheses in the past 3 mo according to their electronic medical record. All outcomes were measured at individual level.

Sample Size
To estimate the required sample size, we used a method that takes into account potential clustering of effects within practices, the expected difference in outcome between intervention groups and the required power of the study. Sample size calculation was done with nQuery Advisor (Statistical Solutions, http://www.statsol.ie/html/nquery/nquery_home.html). A related study completed in occupational health care showed a difference of 15% in full return to work after a period of three months [24], which we considered to be a relevant difference for our trial. Expecting a proportion still on sick leave after 3 mo of 21% in the MISS group and 36% in the UC group, the sample size needed in each group was 126 (with a power of 80% at a 0.05 level two-

sided log-rank test for equality of survival curves). Taking into account an intracluster correlation coefficient of 0.025 because of randomisation at physicians' level and seven patients per cluster, a total of 290 patients was needed. Assuming a dropout rate of 30% (approximately 10% at each moment of follow-up), enrolment of 415 patients was needed.

Randomisation and Blinding

The PCPs were randomly allocated at four different recruitment moments, with block sizes of n = 10, n = 7, n = 14, and n = 15. A standard procedure was followed to conceal allocation: the names of the PCPs (and dummy in an uneven group) were put on a list in random order. Independently, a randomly ordered list of codes (1 = MISS, 2 = UC) was generated. These lists were brought together and the first PCP on the list was allocated to the group indicated by the first code, and so on. As a result, 24 PCPs were allocated to the MISS group and 22 to the UC group. After the PCPs were assigned and the MISS group had received 7 h of training, the patients were enrolled by screening the source population. Patient selection was performed by the research team, in order to prevent selection bias due to the MISS training. The PCPs gave entrance to the names and addresses of the source population, and the source population was given the inclusion criteria through a screening questionnaire. The research assistance team contacted the patients who returned the questionnaire by phone, gave information about the study, and was responsible for the final recruitment. The internal research team, responsible for the process of data collection, knew the study involved was a randomised controlled trial, but they had no information on which PCP was allocated to what condition. Patients and external interviewers were blinded. They were kept unaware that two different groups were formed, and were told that the study was about stress and sick leave.

Statistical Methods

To evaluate the effectiveness of the MISS compared to UC, we used Cox regression analysis in STATA 8.0 (Stata, http://www.stata.com/stata8/) with robust standard errors [25] on our primary outcome measure. Differences in duration of sick leave were expressed as hazard ratios (HRs) and corresponding confidence intervals (95% confidence interval [CI]) for the MISS group, compared to the UC group. Estimates of the intervention effects on our secondary outcome measure were obtained from linear mixed models in SPSS 12.0 (SPSS, http://www.spss.com).

All analyses were conducted according to the intention-to-treat principle and corrected for the clustered design. The analyses were performed in several stages. First, baseline similarity of the two groups was examined for all potential confounders (age, gender, marital status, level of education) and baseline values of symptom scores (distress, depression, anxiety, and somatisation). Secondly, the unadjusted association between the groups (MISS versus UC) and both outcome measures were calculated. This association was then adjusted for each of the potential confounders separately. A forward selection procedure was followed to include the potential confounders. For our primary outcome measure this was done in order of highest change in the regression coefficient. Only those factors that changed the regression coefficient by more than 10% were considered to be confounders, and retained in the model. For our secondary outcome measure this was done by checking the significance of the p-values. Confounders were retained if they significantly contributed to the model ($p < 0.05$). Furthermore, we were interested in potential modification of the treatment effects by the PCPs' diagnosis of SMD, and therefore preplanned subgroup analyses on diagnosis in the

Cox regression analysis and linear mixed models effect evaluation. Baseline measures of self-reported symptoms, as well as diagnoses from the electronic medical records were examined, so we were able to check for classification of patients and severity of complaints (inclusion is only by self-reported level of distress with sick leave). We added product terms for the possible effect-modifier “diagnosis” (with categories SMD, other mental health problems, or somatic health problems) and condition (MISS or UC) to the model and checked for significance of the interaction term ($p < 0.10$). If significant, we proceeded with subgroup analyses. Since the diagnostic behaviour of the PCPs in the MISS group might have been changed as a result of the training, we were aware of confounding by selection bias. If the MISS PCPs detected more patients with an SMD than their UC counterparts, they would possibly detect a significantly higher proportion of patients with relatively mild disorders, which in itself could explain any differences in the patient outcomes of the groups. Therefore, we tested again for confounding of the association between the intervention and the outcome by baseline values of symptom scores (distress, depression, anxiety, and somatisation).

Results

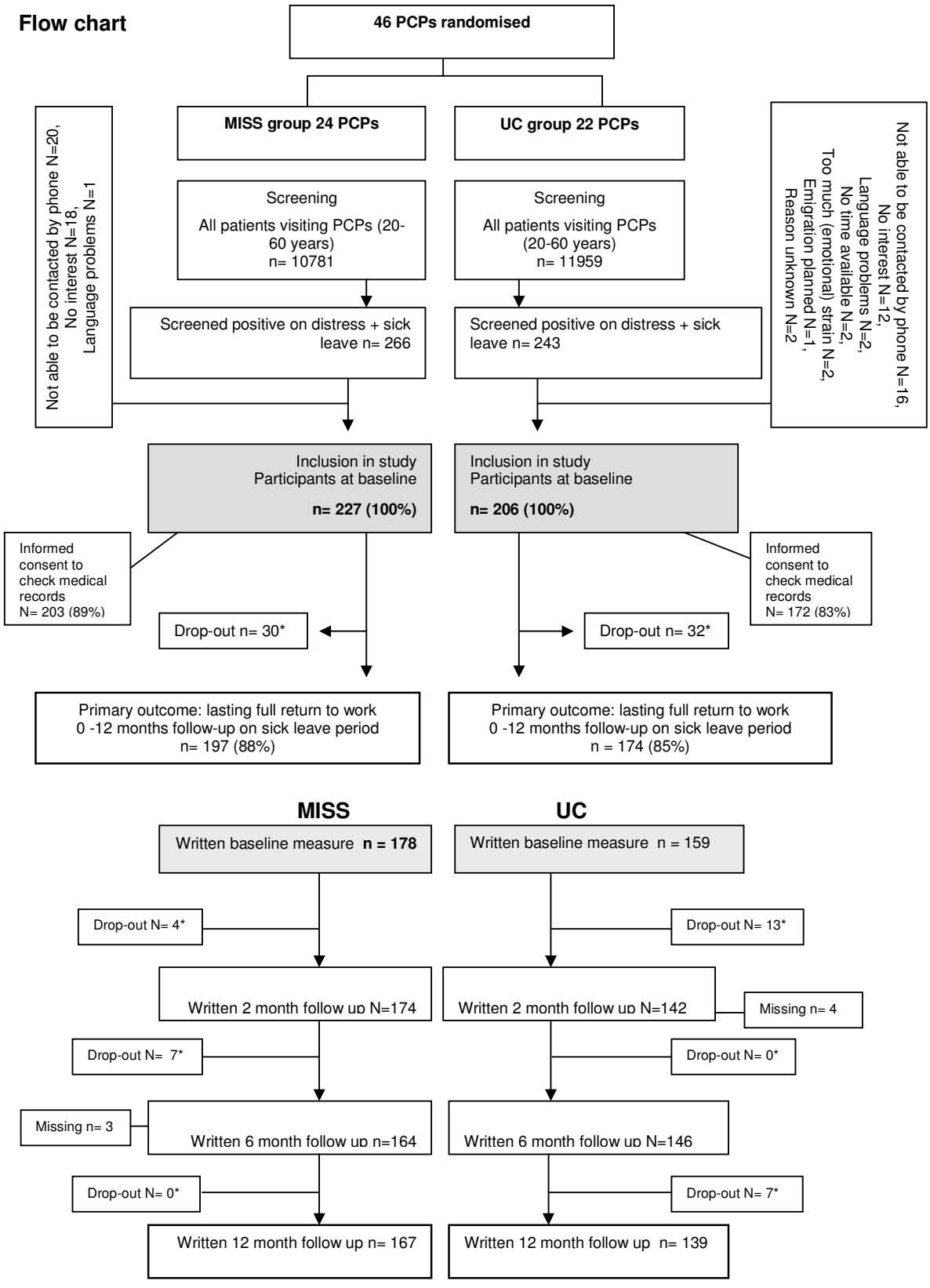
Participant Flow, Baseline Data, and Numbers Analysed

Between September 2003 and October 2004, a screening letter was sent to the source population of 22,740 patients. The overall response percentage on our screening method was 51.5%; this was measured in a group of 336 randomly selected attenders. A total of 433 patients (1.9% of 22,470) were included in the study, 66.3% of whom were women.

Table 1 shows that baseline demographics and clinical characteristics of patients were largely similar, and only a small difference in level of education was found. The mean number of visits to the PCP, counted from the day of sick leave up to 3 mo, was 2.55 (standard deviation [SD] 2.12) in the MISS group, and 2.50 (SD 2.23) in the UC group ($p = 0.839$). With regard to clinical characteristics, baseline measures of self-reported symptoms were taken into account. Up to 80% of the patients scored above threshold on self-reported symptoms of distress, almost half scored above threshold on symptoms of depression, and about one-third scored above threshold on symptoms of anxiety. Symptoms of somatisation also were above threshold in more than half of the patients.

The participant flow from baseline up to 12 mo follow-up is represented in a Flow Chart. For our primary outcome measure—duration of sick leave—data on 197 of the 227 (87%) of the patients from the MISS group and 174 of 206 (84%) of the patients from the UC group were available. During follow-up, 44 (19.4%) of the patients in the MISS group and 47 (22.8%) of the patients in the UC group withdrew from the study (see Flow chart). Only small differences were found with regard to baseline demographics and the clinical characteristics measured with the 4DSQ scores between the drop-outs and completers.

Flow chart



*Reasons for **overall drop-out (MISS n = 44/ 19.4%; UC n= 47/ 22.8%)** were:
'no time or too busy' (MISS n= 9, UC n= 5), 'burden too heavy' (MISS n =7, UC n=7), 'no longer willing to participate' (MISS n= 10, UC n=13), 'moved' (MISS n=3, UC n=3), 'lost to follow-up' (MISS n=10, UC n=15), 'no distress' (UC n=1) or unknown (MISS n=6, UC n=5).

Table 1. Characteristics of patients with SMD symptoms and < 3 months sick leave

Patients baseline measures		**MISS (N=227)**	**Usual Care (N=206)**
Women N (%)		153 (67)	134 (65)
Mean age (SD)		41.97 (8.8)	39.50 (9.6)
Married or cohabiting N (%)		174 (77)	148 (72)
Level of education N (%)			
	Low	59 (27)	46 (22)
	Intermediate	94 (42)	102 (50)
	High	70 (31)	57 (28)
Mean (SD) number of visits to the PCP, counted from the day of sick leave + 3 months		2.55 (2.12)	2.50 (2.23)
4DSQ scores available*		MISS N= 180 (80%)	UC N= 161 (78%)
Distress	N above threshold (%)	140 (78.2)	131 (81.9)
Depression	N above threshold (%)	86 (48.0)	72 (45.0)
Anxiety	N above threshold (%)	54 (30.2)	48 (30.0)
Somatization	N above threshold (%)	103 (57.5)	86 (53.7)

*See Table 3 for mean scores, score ranges and elevated level scores.

Table 2. Median number of days of sick leave before lasting full return to work*

MISS Number of days (95% CI)	**N=**	**Usual Care** Number of days (95% CI)	**N=**	**Hazard ratio (95% CI)**	**P-value**
96 (81-111)	*197*	102 (75 – 182)	*174*	**1.06 (.87 - 1.29)**	0.562

*Since the duration of sick leave does not have a normal distribution, we report the median number of days

Outcomes and Estimation

All analyses were adjusted for the clustering effect of PCPs. Tables 2 and 3 present the scores for primary and secondary outcome measures. Analysis showed no superior overall effect of the MISS on our primary outcome measure, days of sick leave (unadjusted HR 1.06, 95% CI 0.87–1.29; see Table 3). The median number of sick leave days before return to work was 96 (95% CI, 81–111) in the MISS group and 102 (95% CI, 75–182) in the UC group. Multilevel analyses showed that the analyses on our secondary outcome measure needed to be adjusted for the correlation of repeated measures within patients. Over 12 mo follow-up, the severity of all symptoms was reduced significantly in both groups ($p < 0.001$), and on our secondary outcome measure no significant differences were found between the MISS group and the UC group. A considerable number of patients still scored above threshold on self-reported symptoms after 12 mo follow-up. As can be seen in Table 3, this accounts for around 40% of the patients on symptoms of distress, and about one-quarter of the patients on symptoms of depression.

Table 3. Symptom scores at follow-up

4DSQ scores	ICC	p =		MISS	Usual Care	F	p-value
Distress mean (SD)	*0.028*	*0.107*				*1.213*	*0.304**
Score range: 0- 32			*Baseline*	19.21 (8.5)	18.79 (8.1)		
Elevated level; score >10			*2 month follow up*	14.26 (9.37)	15.24 (8.84)		
			6 month follow up	11.73 (9.08)	13.16 (9.06)		
			1 year follow up	10.81 (8.91)	10.49 (8.64)		
N above threshold (%) after 1-year follow-up				*75 (44.9%)*	*55 (39.6%)*		
Depression mean (SD)	*0.015*	*0.206*				*0.332*	*0.802**
Score range: 0-12			*Baseline*	3.46 (3.7)	3.38 (3.6)		
Elevated level; score >2			*2 month follow up*	2.54 (3.53)	2.59 (3.50)		
			6 month follow up	2.11 (3.31)	2.20 (3.25)		
			1 year follow up	1.74 (2.92)	1.89 (3.04)		
N above threshold (%) after 1-year follow-up				*40 (24.0%)*	*40 (28.8%)*		
Anxiety mean (SD)	*0.021*	*0.219*				*0.899*	*0.441**
Score range: 0-24			*Baseline*	5.51 (5.5)	5.41 (5.5)		
Elevated level; score > 7			*2 month follow up*	4.19 (5.32)	4.74 (5.61)		
			6 month follow up	3,12 (4.63)	4.03 (5.20)		
			1 year follow up	2.83 (4.55)	3.14 (4.54)		
N above threshold (%) after 1-year follow-up				*23 (13.8%)*	*18 (12.9%)*		
Somatization mean (SD)	*0.048*	*0.054*				*1.295*	*0.275***
Score range: 0-32			*Baseline*	12.88 (6.9)	12.35 (6.8)		
Elevated level; score > 10			*2 month follow up*	11.22 (8.01)	10.96 (7.26)		
			6 month follow up	9.76 (7.48)	10.33 (6.87)		
			1 year follow up	8.34 (6.67)	9.00 (6.96)		
N above threshold (%) after 1-year follow-up				*51 (30.5%)*	*46 (33.6%)*		

*adjusted for age, **adjusted for age and level of education.
MISS baseline N= 180 (80%), 2-month follow-up N =174 (76.7%), 6-month follow-up N=164 (72.2%), 1-year follow-up N = 167 (73.6%) / UC baseline N= 161 (78%), 2-month follow-up N= 142 (68.9%), 6-month follow-up N= 146 (70.9%), 1-year follow-up N=139 (67.5%)

Ancillary Analyses

The baseline diagnoses from the medical records are shown in Table 4, divided into three categories: SMDs, other mental health problems, and somatic problems. As can be seen in Table 4, more PCPs in the MISS group recognised patients as having SMD (p = 0.068). These diagnosis categories showed interaction with the intervention in the Cox regression analysis on differences in duration of sick leave (p = 0.033). The PCPs' diagnosis of both SMDs and other mental health problems was associated with a longer median duration of sick leave, compared to the diagnosis of somatic health problems.

Table 4. Diagnosis by primary care physician at baseline

Diagnosis*	**MISS**	**UC**
SMD n (%)	90 (45)	66 (39)
Other mental health problems n (% within category)	67 (33)	49 (29)
• *Depression*	*24 (36)*	*17 (35)*
• *Anxiety states; panic disorder*	*5 (7)*	*1 (2)*
• *Threshold psychiatric disorders*	*7 (10)*	*5 (10)*
• *Non-specific distress*	*9 (13)*	*12 (24)*
• *Somatoform problems*	*8 (12)*	*3 (6)*
• *Social and/or private problems*	*15 (22)*	*12 (24)*
Somatic problems n (% within category)	44 (22)	56 (33)
• *Pain in back, neck or upper extremities*	*28 (64)*	*32 (57)*
• *Gastrointestinal, respiratory, cardiovascular, digestive or dermatological problems.*	*16 (36)*	*24 (43)*

*Chi-squared, p = 0.068

Table 5 shows the subgroup analyses, and among patients diagnosed with SMDs, time to return to work was shorter in the MISS group than in the UC group (unadjusted HR 1.49 [0.98–2.26], and adjusted HR 1.72 [1.18–2.51]). The HRs for return to work in the subgroups other mental health problems and somatic problems slightly favoured the UC group. However, these differences were small and not statistically significant. For our secondary outcome measure, severity of symptoms, the interaction of intervention with diagnosis showed no significant results, so no subgroup analyses were performed. Although the subgroup analyses were planned out before the trial took place, in no case can this result be regarded as evidence for a difference between the MISS group and UC group.

Table 5. Median number of days of sick leave before lasting full return to work, by subgroups

Subgroups of diagnosis#	**MISS** Number of days (95% CI)	**N=**	**Usual Care** Number of days (95% CI)	**N=**	Unadjusted Hazard ratio (95% CI)	P-value	Adjusted Hazard ratio (95% CI)	P-value
Stress-related mental disorder	97 (75- 119)	*90*	170 (143 – 197)	*66*	**1.49** (0.98 - 2.26)	0.060	**1.72** (1.18 - 2.51)	0.005[1]
Other mental health problems	109 (86 – 132)	*67*	75 (32 – 118)	*50*	**0.91** (0.61-1.36)	0.638	**0.81** (0.46 - 1.40)	0.445[2]
Somatic problems	78 (13- 143)	*44*	21 (8 – 34)	*56*	**0.73** (0.49-1.07)	0.106	**0.76** (0.47 - 1.12)	0.159[3]

#Chi-squared, p= 0.033

[1]HR adjusted for baseline values for distress.

[2]HR adjusted for baseline values for age, level of education and anxiety.

[3]HR adjusted for baseline values for anxiety**.**

Discussion

Interpretation

We were unable to prove our hypothesis that the MISS would be more effective than UC, either on our primary outcome measure nor on the secondary. The median number of days on sick leave before return to work was substantial in both groups and a considerable number of patients still scored above threshold on the self-reported symptoms. However, the severity of symptoms was reduced significantly during the 1 y follow-up.

The MISS did not show an overall effect in our study sample of patients with symptoms of distress on sick leave. Possible explanations for the failure to find an effect can be sought within the patients, the PCPs, and the intervention used. First of all, we shall discuss the patients. There might have been a problem with the inclusion criteria used. It is possible that we misclassified a substantial part of the patients because our criteria might have been much too broad at both sides of the severity continuum. As can be seen with the self-reported symptoms of depression, 24.0% in the MISS group and 28.8% in the UC group still scored above threshold level after one year. This substantial group of patients may have had conditions that were of a more chronic nature (e.g., depressive disorder) and needed more extensive care. The difficulty here is that relevant dimensions of psychopathology that are subacute, but not yet chronic, and clearly related to stress (e.g., SMD), could not be distinguished in a straightforward way from more severe psychopathology or from an admixture of somatic and psychological symptoms. Nevertheless, we used only three questions on distress symptoms and one question on sick leave to recruit patients who had visited their PCP. We were convinced of the importance of undertaking this study, and for that reason might have underestimated the challenge of diagnosing SMDs. Thus, it is clear that the evidence base on criteria for the diagnosis of SMD in patients has to grow substantially.

Table S1. Baseline scores on 4DSQ symptoms, and number of visits to the PCP, stratified into subgroups

	MISS	UC
Subgroup SMD		
Distress	20.56	19.08
Depression	3.94	2.64
Anxiety	6.31	4.50
Somatization	14.52	10.86
Mean # of visits to the GP[1]	2.60	2.34
Subgroup other mental health problems		
Distress	17.47	20.41
Depression	2.89	3.93
Anxiety	4.69	6.41
Somatization	10.25	14.54
Mean # of visits to the GP[1]	3.13	3.20
Subgroup somatic diagnosis		
Distress	17.80	17.03
Depression	2.80	2.74
Anxiety	6.12	3.84
Somatization	12.64	12.14
Mean # of visits to the GP[1]	2.03	1.88

[1] Counted from the day of sick leave + 3 months

Furthermore, the lack of effect might be due to the PCPs. They are the gatekeepers of health care and have extensive workloads. The MISS takes into account the time constraints under which a PCP works, as well as the position of a PCP as a generalist who does not have the capacity to apply highly specialised interventions. Nevertheless, the PCPs may have been too busy to carry out any intervention at all. Alternatively, the intervention might have been too minimal, or the training hours too short for the PCPs to actually learn the necessary skills. Unfortunately, except for detection and labelling of symptoms, the extent to which the PCPs actually applied their skills was not addressed in this study.
Ancillary analyses showed there was an interaction between the intervention and detection of SMDs, other mental health problems, or somatic problems. Both SMDs and other mental health problems were more frequently diagnosed by the PCPs in the MISS group than by the PCPs in the UC group. Since, as a result of the training, the MISS PCPs were more sensitive to mental disorders and more keen to diagnose SMDs in particular, it seems logical to expect that this result would be biased. It seems likely that the SMD patients in the MISS group were significantly less severely affected than the SMD patients in the UC group. This in turn could have caused differences in outcome of the SMD patients in the study group, giving a false (confounded) impression of the effect of the MISS. However, the SMD patients in the MISS group actually turned out to have higher baseline levels of symptoms than the SMD patients in the UC group (see Table S1). We tested baseline variables for confounding and as a result controlled for severity of symptoms, but that did not make the effect of the intervention in the SMD patients disappear. Nevertheless, it should be noted that this was an ancillary analysis, and because of the selection of the SMD patients by the PCPs' diagnosis, although it was a preplanned subgroup analysis, in no case can this result be regarded as evidence of a difference between the MISS group and UC group.

Generalisability
We carried out a randomised controlled trial with only a few exclusion criteria and thereby allowed considerable variation due to context, diagnosis, and treatment, so flattering performances or overestimation of application are unlikely to be issues. Instead, the considerable variation increases the relevance of our results because it reflects routine clinical practice instead of ideal circumstances.

Overall Evidence
As far as we know, this is the first randomised controlled trial to evaluate the effects of an intervention in primary care for SMDs with sick leave as a primary outcome. At the start of our study, the only comparable study had been performed in occupational health care by Jac van der Klink et al. [24], who reported high return-to-work rates after three months (78% in the intervention group and 63% in the UC group, $p = 0.02$). In our study, these rates were lower (51% in the MISS group and 57% in the UC group, $p = 0.239$). In the meantime, the results of one other randomised controlled trial performed in primary care have been published [1]. In that trial, social workers were trained to apply the intervention, while PCPs provided UC for patients in the other group. The study found no differences between the conditions. Return-to-work rates after three months were 37% in the intervention group and 40% in the UC group. The more favourable outcomes of this study seem to indicate that the occupational setting may be exceptional, and that the results may not equally apply to primary care. Moreover, our trial addressed a wider range of patients than the trial of van der

Klink et al., who excluded patients with major depression or anxiety. The more beneficial effects of the MISS among patients with a PCP's diagnosis of SMD may indicate that these patients more strongly resemble the participants in the occupational study.

Conclusions

This project represents a further step in the development of an evidence-based intervention for the treatment of distressed patients on sick leave. We were unable to show an effect of the MISS on duration of sick leave. In subgroup analyses a possible direction for further research was identified: namely, whether patients diagnosed with SMDs may benefit from an effect of the MISS on duration of sick leave. We feel that emphasis on functional rehabilitation of the patient is important, because continuation of sick leave may lead to chronicity and deterioration of symptoms. Unfortunately, diagnosis of SMD in primary health care turns out to be less straightforward than we expected, and the evidence base on criteria for this diagnosis will need to grow substantially before definite conclusions can be drawn. Researchers should take into account the importance of a diagnostic work-up to differentiate between common mental health problems, because there is still a lack of generally accepted criteria to diagnose "uncomplicated SMD" as a level of psychopathology.

Furthermore, continuing research should focus on the potential beneficial effects of the MISS; we need to investigate which elements of the intervention might be useful and which elements should be adjusted to make the MISS effective.

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5

Cost-effectiveness of a minimal intervention strategy for stress-related sick leave in general practice: results of an economic evaluation alongside a pragmatic randomized controlled trial

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Abstract

Objective: The objectives were to: 1. determine the cost-effectiveness of a general practitioner-based minimal intervention strategy for stress-related sick leave in reducing sick leave days compared to usual care; 2. evaluate the cost-effectiveness in terms of improving quality-adjusted life years; and 3. determine the potential cost offset.

Methods: An economic evaluation from a societal perspective was conducted alongside a pragmatic, cluster-randomized controlled trial with a 12-month follow-up. Analyses were based on complete cases. Uncertainty around cost differences and incremental cost-effectiveness ratios were estimated by nonparametric bootstrapping, cost-effectiveness planes and acceptability curves. Sensitivity analyses, including multiple imputation of missing values and alternative valuations of productivity gains were conducted. Ancillary analyses based on preplanned subgroups were performed.

Results: There were no significant differences in outcomes or costs. The incremental cost per day less of gross sick leave was € 33, and per QALY, € 76,046. The potential cost offset ranged from a loss of € 135 to a savings of € 1369. Results of the sensitivity analyses were similar to the main findings. Ancillary analyses suggested that the intervention may be cost-effective for the subgroup, stress-related mental disorders.

Conclusions: Although there was no statistically significant evidence that the minimal intervention strategy was clinically or economically superior to usual care, it may a promising intervention for the subgroup, stress-related mental disorders. Future research is needed to confirm this observation. Also, in order to improve the meaningfulness of future studies, further attention to how health-related productivity changes are measured and valued is needed.

Introduction

Poor mental health is a widespread phenomenon. The prevalence of mental health problems in the working population has been reported to range between 10-18% [1-3], and it has been estimated that by 2020, the global burden will be second only to ischemic heart disease [4]. In up to 90% of all workers with mental health problems, stress has been identified as the underlying cause [5,6]. Moreover, mental health problems can have a negative effect on quality of life, and lead to suboptimal productivity with considerable socioeconomic consequences [7]. An upward trend of stress-related sick leave and early retirement has been reported across the European Union [8]. The annual cost of sick leave and productivity loss in the U.S.A. has been estimated around $200 billion [9]. In The Netherlands, one-third of all long-term sick leave or work disability cases are attributable to stress-related mental health problems, and in 2004, approximately € 3 billion in disability benefits were paid out to individuals with this problem [10-12].

Worldwide, 60-95% of those with mental health problems first seek assistance in primary care [13]. In The Netherlands, the key point of contact is the general practitioner (GP). While stress-related mental health problems can significantly affect an individuals' ability to work and result in (prolonged) sick leave, this functional aspect is often not addressed by GPs [14].

Recently, a pragmatic, cluster-randomized controlled trial with a 12-month follow-up was conducted in the primary care setting to evaluate the effectiveness of a minimal intervention strategy for stress-related mental disorders with sick leave (MISS) for GPs compared to usual care (UC) [15]. Although the MISS was not found to be more effective than UC in reducing the time to lasting full RTW, a positive economic impact may still exist with respect to total sick leave, quality of life, and differential use of resources and cost offsets. Thus, the three objectives of this study were to determine: 1. the cost-effectiveness of the MISS in reducing total sick leave days compared to UC; 2. the cost-effectiveness of the MISS in improving quality-adjusted life years compared to UC; and 3. the potential cost offset of MISS compared to UC.

Methods

Study design

An economic evaluation was conducted from a societal perspective alongside a pragmatic, cluster-randomized controlled trial with a 12-month follow-up. The protocol was approved by the medical ethical committee of the VU University Medical Center (Amsterdam, The Netherlands), and details of the study design and the minimal intervention strategy for stress-related mental disorders with sick leave (MISS) have been reported elsewhere [16]. A brief overview is presented below.

MISS

Recently, an activating approach for occupational physicians for the treatment of workers with adjustment disorder was found effective in the occupational health care setting [17]. This approach was customized to the general practice setting, with particular attention to practicing physicians' time constraints and nature as generalists. It was designed to equip GPs with skills to perform five key tasks within three consultations to help activate patients on stress-related sick leave to return to work. The five tasks were: 1. diagnosing stress-

related mental disorders; 2. providing education about the problem and importance of taking an active role in one's functional recovery; 3. advising patients on how to reflect, cope and problem-solve; 4. monitoring progress; and 5. referring to specialists.

Participants

GPs were recruited at four different time points, and at each moment, those consenting to participate were randomized to either usual care (UC; N = 22) or MISS (N = 24). The GPs who were randomized to the MISS group followed an 11-hour course consisting of two 3.5-hour training and two 2-hour follow-up sessions. The training was provided by the developer of the MISS intervention and an experienced occupational physician.

Participants were recruited by the researchers from a source population accessed via participating GPs' computerized medical record systems. Patients who had a severe psychiatric disorder (i.e. mania or psychosis), a terminal illness, or poor command of the Dutch language were excluded by the GPs. Remaining patients who had a consultation during the previous one to two weeks and were aged between 20 and 60 years, were mailed an information packet about the study along with a screening questionnaire. If the responses on the returned screening questionnaires were positive for a moderately elevated distress level (as measured by three questions of the Four Dimensional Symptom Questionnaire (4-DSQ) distress scale [18]), gainful employment, as well as (partial) sick leave for no longer than three months, the respective patient was contacted by telephone. Enrollment in the study was finalized during the telephone contact, following verification of the inclusion criteria and receipt of oral informed consent. Written informed consent for participation and access to the subject's medical records was obtained separately.

Outcomes

A combination of telephone interviews and questionnaires were used to collect outcome data at baseline and 2-, 6- and 12-months follow-up. The number of sick leave days beginning from the first day of sick leave to 1-year thereafter was used as the outcome in the cost-effectiveness analysis (CEA). The quantity of sick leave days was operationalized in two ways: gross and net. The former was defined as the total number of calendar days that subjects were completely or partially sick-listed, and the latter accounted for partial return-to-work [19]. Quality-adjusted life years (QALY) was the outcome in the cost-utility analysis (CUA). Quality of life was measured by the EuroQol-5D [20], and the QALYs for the 12-month follow-up were computed by multiplying the utilities [21] by the time spent in the given health state, and then linearly interpolating the transitions between the four measured health states [22].

Resource use

GP consultations and laboratory tests were extracted from the computerized medical records for a 12-month period starting from the first day of sick leave. Data on additional resource use over 4-week periods were collected via telephone interviews and questionnaires at baseline and 2-, 6- and 12-months follow-up. These data were extrapolated over 12-months by linear interpolation.

Valuation

The cost prices used for valuation are presented in Table 1. Wherever possible, the volume of resource use was valued using standard cost prices according to Dutch Manual for

Table 1: Cost prices used for valuation of resource use in the economic evaluation (Year 2004)

Units [Units of measurement]	Cost price
Health care sector	
Primary Care	
General practitioner	
Office consultation [No.]	€ 20.44 *
Telephone consultation /renewal of prescription [No.]	€ 10.22 *
House call [No.]	€ 40.88 *
After-hours telephone consultation [No.]	€ 24.30 †
Diagnostic tests	
Blood [No.]	€ 21.66 *
Urine [No.]	€ 14.42 *
X-rays [No.]	€ 49.80 ‡
Other diagnostic tests [No.]	Variable †
Psychologist in private practice [No. of sessions]	€ 76.90 *
Social worker [No. of sessions]	€ 48.43 †
Physical therapist [No. of sessions]	€ 23.02 *
Other paramedical professionals [No. of sessions]	Variable ‡
Medications [per medication]	Variable §
Secondary Care	
Regional Institute for Community Mental Health Care (including Drug & Alcohol Abuse Centre) [No. of sessions]	€ 125.47 *
Hospital-based psychiatrist – [No. of sessions]	€ 64.18 *
Part-time psychiatric day programs - General hospital [No. of sessions]	€ 90.58 *
Medical specialist – Outpatient [No. of consultations]	€ 56.66 *
Medical specialist – ER [No. of consultations]	€ 140.64 *
Hospitalization – General hospital [No. of days]	€ 340.99 *
Professional home health care [per hour, all services]	€ 31.06 *
Professional family home assistance [per hour]	€ 27.10 *
Alpha help [per hour]	€ 12.85 *
Other sector	
Occupational physician [No. of consultations]	€ 21.50 ‡
Patient/family	
Alternative care [No. of sessions]	Variable ‡
Support group/self-help courses [No. of sessions]	Variable ‡
Informal help [per hour]	€ 8.40 *
Productivity losses	
Sick leave from paid work [per day]	€ 254.81 ¶
Intervention costs	
Training costs for MISS [per MISS subject]	€ 120.46 **

Cost price sources: * Dutch Manual for Costing; † Dutch Central Organization for Health Care Charges (CTG) ;‡ Respective providers or professional organizations; § Royal Dutch Society for Pharmacy; ¶ Per hour cost price from the Dutch Manual for Costing converted to day cost price according to a 36-hour work week; ** Determined via a bottom-up calculation.

Costing [23]. If standard cost prices were not available, tariffs, or an average price according to providers or professional organization, were used. Medication costs were determined Productivity loss costs were estimated from a societal perspective by both the Friction Cost Method (FCM) and Human Capital Approach (HCA) [25,26]. According to the FCM, productivity losses are limited to the time (i.e. friction period) needed to restore production back to its initial level (i.e. time needed to find and train a replacement), which can be shorter than the actual sick leave duration of the ill worker [26]. In this study, an average friction period of 154 days was used. Productivity loss costs were estimated by multiplying the gross number of sick leave days (up to a maximum of 154 days) by an average daily wage and an elasticity of 0.8 that reflects a less than proportional decrease in productivity with respect to time worked in the Dutch context [23]. Under the HCA, no such assumptions are made, and the productivity loss costs are estimated by multiplying the total gross number of sick leave by an average daily wage.

Data analysis

The economic evaluation was performed according to the intention-to-treat principle, and the main analyses were based on cases with complete cost and outcome data. The effect of MISS compared to UC on QALYs and resource use were assessed using t-tests and chi-square tests (SPSS version 12.0.2). The mean cost and sick leave differences were determined and respective 95% confidence intervals were obtained by bias corrected and accelerated (Bca) bootstrapping with 2000 replications [27]. For the cost-effectiveness

Table 2: Overview of the bottom-up calculation of the training costs for the MISS group.

Resources	Description	Aggregated cost
Trainer costs	Two trainers for all four training series, including preparation.	€ 12,830.40
GP attendance	Time (11 contact hours) of each GP invested to follow the MISS training.	€ 9,467.04
Travel costs	Average return travel to Amsterdam (60 km) and parking for each training session.	€ 1,823.96
Room/equipment/refreshment costs	For rental of meeting room at VU University campus. Equipment includes projector, screen & flip board. Refreshments during breaks.	€ 3,082.50
Study material for 24 GPs	Binder, dividers & 75 printed pages	€ 140.52
	Total training costs	€ 27,334.41
	Average cost per MISS subject	€ 120.46

analysis (CEA), the difference in the investment costs (i.e. sum of total direct and training costs) between the MISS group and UC was divided by the difference in gross number of sick leave days. Note that productivity loss costs due to sick leave were not included in the costs as the difference in sick leave was the effect of interest. In the cost-utility analysis (CUA) comparing MISS to UC, the difference in total costs (i.e. the sum of investment costs,

and productivity loss costs estimated by the FCM) was divided by the difference in QALYs. The 95% confidence intervals around the ratios were calculated by a bias-corrected percentile bootstrapping method [28], the bootstrapped cost-effect pairs were plotted in a cost-effectiveness plane [29], and acceptability curves were generated [30]. Lastly, the potential cost offset of the MISS compared to UC was investigated by weighing the relevant investment costs against alternative valuations of productivity gains.

Sensitivity analysis

Four sensitivity analyses were conducted to test the robustness of the main results. First, the CEA was repeated with the difference in net number of sick leave days as the effect measure, in the denominator. Second, the CUA was repeated with the difference in total costs where the productivity loss cost component was estimated by the HCA, in the numerator. Third, the analyses were repeated following multiple imputation of missing cost and outcome data based on a Multivariate Imputation by Chained Equations (MICE) procedure [31]. Lastly, the potential cost offset was determined from a company's perspective.

To evaluate the cost offset from a company's perspective, 'Other sector' costs were weighed against four valuations of productivity gains. The four methods used were: 1. HCA using the gross number of sick leave days; 2. HCA using the net number of sick leave days to take into consideration that workers are productive when they (resume) work on a part-time basis; 3. the net HCA estimation multiplied by a median wage multiplier of 1.28, which reflects recent findings that the cost to a company due to missed work is often greater than an estimation based on wage loss [32]. This is related to three key characteristics of a given function: the ease with which a perfect replacement can be found, the extent to which work is performed as part as a team and the time sensitivity of the output [33]; and 4. the net HCA estimation multiplied by an elasticity of 0.55, reflecting the assumption that productivity loss may be tempered by compensation by workers on their return, or by colleagues [34].

Ancillary analysis

Ancillary analyses were conducted for three pre-planned subgroups that were identified from the total study population according to the GPs' diagnosis and/or working hypothesis extracted *a posteriori* from their electronic databases. The first subgroup, stress-related mental disorder (SMD), referred to those with elevated yet uncomplicated distress or, in other words, the absence of a depressive or anxiety disorder, and resembling adjustment disorders, neurasthenia or nervous breakdown. The second, other mental health problems (Other MHP), referred to those who present with mental health problems, including anxiety or depressive disorders in addition to elevated distress. The third, somatic problems (SP), included those who have physical complaints along with elevated distress levels.

Results

Patients and data availability

Between September 2003 and October 2004, a screening letter was sent to the source population of 22,740 patients. Ultimately, 433 patients enrolled in the study (MISS = 227; UC = 206), and the overall number of drop-outs was 91 (21%; MISS = 44; UC = 47). No significant differences were observed in demographic characteristics (i.e. age, gender,

education level or marital status) nor baseline symptom severity between the drop-outs and completers.

Table 3: Means and standard deviations (S.D.) of resource use and utilization rate (%) per group during the 12-month follow-up

Units [Units of measurement]	MISS (N = 109)			UC (N = 83)		
Health care sector	**Mean**	**S.D.**	**%**	**Mean**	**S.D.**	**%**
Primary Care						
General practitioner						
Office consultation [No.]	6.1	4.5	95.4%	6.3	4.7	96.4%
Telephone consultation /renewal of prescription [No.]	0.2	0.5	15.6%	0.2	0.6	12.0%
House call [No.]	0.0	0.1	1.8%	0.0	0.2	3.6%
After-hours telephone consultation [No.]	0.1	0.2	6.4%	0.1	0.4	8.4%
Diagnostic tests						
Blood [No.]	0.4	0.7	28.4%	0.3	0.6	26.5%
Urine [No.]	0.3	0.8	14.7%	0.2	0.6	13.3%
X-rays [No.]	0.1	0.4	11.0%	0.2	0.5	16.9%
Other diagnostic tests [No.]	0.1	0.6	2.8%	0.0	0.3	1.2%
Psychologist in private practice [No. of sessions]	4.1	8.0	38.5%	2.6	5.3	28.9%
Social worker [No. of sessions]	1.6	3.6	23.9%	1.2	2.7	25.3%
Physical therapist [No. of sessions]	5.6	11.6	34.9%	6.7	12.8	41.0%
Other paramedical professionals [No. of sessions]	0.3	1.4	4.6%	0.5	1.7	7.2%
Medications [per medication]	--	--	78.9% *	--	--	62.7%
Secondary Care						
Regional Institute for Community Mental Health Care (including Drug & Alcohol Abuse Centre) [No. of sessions]	1.0	4.9	7.3%	0.6	2.4	7.2%
Hospital-based psychiatrist [No. of sessions]	0.4	1.8	7.3%	0.1	0.9	2.4%
Medical specialist [No. of consultations]	1.8	3.6	34.9%	3.0	4.8	39.8%
Part-time psychiatric day program [No. of sessions]	0.1	0.5	3.7%	0.0	0.0	0.0%
Hospitalization [No. of days]	0.2	0.8	7.3%	0.4	1.6	7.2%
Professional home health care [per hour, all services]	0.5	4.0	1.8%	0.8	7.0	1.2%
Professional family home assistance [per hour]	0.0	0.0	0.0%	0.0	0.0	0.0%
Alpha help [per hour]	0.0	0.0	0.0%	0.0	0.0	0.0%
Other sector						
Occupational physician [No. of consultations]	4.5	4.8	74.3%	4.5	5.1	65.1%
Patient/family						
Alternative care [No. of sessions]	1.5 †	3.9	20.2%	4.1	11.0	27.7%
Support group/self-help courses [No. of sessions]	0.4	2.0	5.5%	1.9	15.6	3.6%
Informal help [per hour]	40.2	69.3	100%	39.1	56.1	100%
Productivity losses						
Gross days of sick leave	120.4	101.0	100%	126.5	115.7	100%
Net days of sick leave	97.5	84.1	100%	98.5	93.1	100%

* Medication utilization rate in MISS group significantly higher than UC (X^2-test; $p < 0.05$).

† Mean number of visits to an alternative care provider in MISS group significantly less than UC (t-test; $p < 0.05$).

For the economic evaluation, sick leave data were available for 371 (86%) subjects, QALYs for 253 (58%), resource use from the computerized medical records for 332 (77%), and other resource use from telephone interviews and questionnaires for 364 (84%). Of the latter, 230

subjects had a complete set of data. GP diagnoses were available for 375 (87%) subjects. In total, there were 192 (44%) complete cases (MISS = 109; UC = 83) available for the CEA and cost offset analysis, and complete data from 184 (42%) subjects (MISS = 103; UC = 81) for the CUA. There were no relevant differences in the aforementioned baseline characteristics between the complete cases and incomplete cases. Furthermore, within the complete cases, no significant between-group differences were observed.

Outcomes

There were no statistically significant differences in gross and net sick leave days over a 12-month follow-up between the MISS group and UC (Table 3). The mean gross difference was 6.2 days (95% CI: -26.5; 36.0) and mean net difference, 1.0 (95% CI: -23.9; 26.4). No statistically significant between-group difference was observed in QALYs (MISS: mean = 0.80, S.D. = 0.15; UC: mean = 0.78, S.D. = 0.17; mean difference: 0.02; 95% CI: -0.03; 0.06).

Resource use

The mean volume of resource use and utilization rates per group over 12-months are presented in Table 3. Except for the difference in mean number of visits to alternative practitioners (MISS: mean = 1.5, S.D. = 3.9; UC: mean = 4.1, S.D. = 11.0; $p < 0.05$), there were no other statistically different findings in health care utilization. All subjects, regardless of group allocation, received help from family members or other informal sources outside the health care sector. Medication use and consultations with the occupational physician ranged from 63% to 79%, and utilization of psychosocially-geared services ranged from 0% to 39%. With the exception of medication use, there were no statistically significant between-group differences in utilization rates ($p < 0.05$).

Table 4: Mean resource use costs per patient per group and mean cost differences (MISS versus UC), in Euros, over the 12-month follow-up.

Resource use categories	MISS (N = 109)		Usual Care (N = 83)		Mean difference	95% CI	
	Mean	S.D.	Mean	S.D		Lower	Upper
Health care sector	1,301.54	1,623.28	1,101.34	1,188.34	200.20	-213.21	562.97
Other sectors	96.26	102.35	95.58	110.55	0.67	-30.96	31.23
Patient/family	421.92	627.09	540.67	732.60	-118.75	-302.27	73.74
Total direct costs *	1,819.72	1,863.88	1,737.59	1,608.90	82.12	-422.63	579.94
Productivity loss costs via FCM †	19,603.07	12,335.96	19,264.86	14,262.41	338.21	-3,416.12	4,292.03
Productivity loss costs via HCA †	30,666.03	25,746.52	32,238.07	29,493.26	-1572.04	-9,604.33	6,110.00
MISS training costs	120.46	--	--	--	120.46	--	--
Total investment costs ‡	1,940.18	1,863.88	1,737.59	1,608.90	202.58	-289.63	710.61
Total costs via FCM §	21,543.25	12,863.52	21,002.46	14,857.05	540.79	-3,195.71	4,838.93
Total costs via HCA §	32,606.21	26,210.87	33,975.66	29,980.54	-1,369.45	-9,213.99	7,267.86

* Total direct costs reflect the aggregation of the costs from the health care sector, other sectors and patient/family.

† The inverse of the difference in productivity loss costs reflect the monetary equivalent in terms of productivity gains of MISS compared to UC from a societal perspective.

‡ The total investment costs from a societal perspective is the sum of total direct costs and MISS training costs.

§ Total costs reflect the aggregation of the total direct costs, productivity loss costs (estimated either by the Friction Cost Method or Human Capital Approach) and MISS training costs.

Costs

The mean costs and mean cost differences are presented in Table 4. Mean health care sector costs were higher for the MISS group while the mean patient/family costs were higher in the UC group. Costs in the category, Other sectors, were similar. The mean costs for the aggregated cost categories, total direct and investment, were higher in the MISS group. The productivity loss costs, and associated total cost estimate, were higher in the MISS according to the FCM, but not the HCA. None of the cost differences were statistically significant.

Cost-effectiveness analysis, cost-utility analysis and cost offset

The difference in costs and effects as well as the incremental cost-effectiveness ratios (ICERs) and the distribution across the cost-effectiveness plane of the 2000 bootstrapped estimates for the main CEA and CUA are presented in Table 5. The bootstrapped cost-effect pairs, and acceptability curves from the CEA are shown in Figure 1 and Figure 2, respectively. The mean incremental cost of MISS compared to UC for a day less of sick leave was € 33 and the mean incremental costs per QALY was € 76,046. The maximum probability that MISS was cost-effective compared to UC was 0.6, reached at a ceiling ratio of € 30. CE-planes and acceptability curves for the CUA are not shown. The potential offset from an mean investment of € 203, ranged from a potential loss of € 135 to a savings of € 1369 (c.f. Table 4).

Sensitivity analysis

Findings of the sensitivity analysis were similar to the main analyses. Following multiple imputation, the mean between-group difference in gross sick leave days and costs were smaller, and the mean between-group difference in QALYs was larger. With respect to the CEA, a shift in cost-effects pairs from the quadrants I to quadrants II (more effective/less costly) was observed. For the CUA, a shift from quadrant IV (less effective/more costly) to II was noted (Table 5). For the same range of ceiling ratios, there was no relevant improvement in probability of cost-effectiveness. The potential offset in savings in productivity loss costs associated with the MISS intervention compared to UC from a company's perspective are presented in Table 6. An investment of less than € 1 may result in an offset from € 142 to € 1571.

Ancillary analysis

The cost, effect and ICER subgroup findings are presented in Table 7. With respect to the SMD subgroup, those in the MISS group incurred significantly less gross and net sick leave days than UC. The mean gross difference was 74.0 days (95% CI: 14.7; 132.9). The direction of the mean differences in gross and net sick leave days, although not significant, was in favor of the UC group for Other MHP (mean gross difference = 22.0 days, 95% CI: -36.5; 83.4), and the difference in the SP group was small (mean gross difference = 4.5 days, 95% CI: -38.1; 49.6). There were no statistically significant between-group differences in QALYs for neither of the subgroups. The cost-effectiveness of MISS shifted toward quadrant I in the SMD group (Figure 1) and the mean ICER suggested that the extra costs for a day

Table 5: Cost differences, effect differences, and incremental cost-effectiveness ratios from the cost-effectiveness and cost-utility analyses from the complete case analysis for the total group and following multiple imputation for missing data.

[*] Refers to the northeast quadrant of the CE-plane, which indicates that MISS is more effective and more costly than UC.

[†] Refers to the southeast quadrant of the CE-plane, which indicates that MISS is more effective and less costly than UC.

[‡] Refers to the southwest quadrant of the CE-plane, which indicates that MISS is less effective and less costly than UC.

[§] Refers to the northwest quadrant of the CE-plane, which indicates that MISS is less effective and more costly than UC.

	Sample size		Cost difference (95% CI)	Effect difference (95% CI)	ICER	Distribution in CE-plane			
	MISS	UC				I [*]	II [†]	III [‡]	IV [§]
Complete case analysis									
Gross sick leave days	109	83	202.58 (-289.63; 710.61)	6.17 (-26.49; 36.02)	32.84	48%	15%	5%	31%
QALY	103	81	1208.93 (-2,785.54; 5,404.51)	0.02 (-0.03; 0.06)	76,046.63	55%	23%	4%	17%
After multiple imputation									
Gross sick leave days	227	206	98.11 (-445.98; 642.20)	2.79 (-17.78; 23.35)	35.19	35%	26%	10%	29%
QALY	227	206	416.52 (-2,249.26; 3,082.30)	0.02 (-0.01; 0.06)	16,723.50	55%	35%	2%	8%

Table 6: Potential cost offset from a company's perspective of MISS compared to UC for the total group with respect to productivity gains reported in 2004 Euros

Investment *		Productivity gains		Potential offset ‡
Relevant resources	**Mean difference (95% CI)**	**Estimation method †**	**Mean gains (95% CI)**	
Occupational physician	0.67 (-30.96; 31.23)	Gross days of sick leave - HCA	1572.04 (-6110.00; 9604.33)	€ 1571.36
		Net days of sick leave - HCA	260.14 (-6942.79; 6271.14)	€ 259.46
		Net days with median multiplier of 1.28	332.97 (-8397.14; 8468.76)	€ 332.30
		Net days with an elasticity of 0.55	143.08 (-3655.95; 3743.87)	€ 142.40

* Relevant resource investment costs from a company's perspective in the Dutch context.
† Methods of estimating productivity loss costs from a company's perspective.
‡ Depending on the socioeconomic context, which may influence the relevant investment costs and the method chosen to estimate productivity loss costs, the actual offset will vary accordingly.

less in gross sick leave was € 4. The probability that the MISS was cost-effective compared to UC approached 1 at a ceiling ratio of € 30 (Figure 2).
With regards to the incremental costs per QALY, the cost-effect pairs of the SMD subgroup were largely found in quadrant II, indicating dominance of the MISS over UC. The potential cost offsets from both a societal and employer's perspective may be considerable for the SMD group, ranging from € 6,832 to € 16,364 for the former and from € 6,982 to € 16,485 for the latter (Results not shown).

Discussion

Affected individuals, their families, the workplace, health care sector and society have much to gain by the development, identification and implementation of effective and efficient care for stress-related mental health problems. To supplement findings of a recently conducted pragmatic randomized controlled trial, this study investigated the efficiency of a new approach for GP management of persons with stress-related mental health problems, the minimal intervention strategy for workers with stress-related sick leave (MISS), compared to usual care.
The first and second objectives were to determine the cost-effectiveness and cost-utility, respectively, of a MISS compared to usual care. There was no statistically significant evidence that the MISS intervention was more cost-effective in reducing sick leave than usual care nor in improving the quality-adjusted life years (QALYs) over a 12-month period. The ancillary analysis indicated that the MISS intervention may be cost-effective for the SMD subgroup for a day of sick leave, and that the MISS is dominant when the incremental costs per QALY are considered. The opposite was observed for Other MHP and SP. These observations are in line with the results found in the effectiveness study and underscore the fact that not all (pre-clinical/mild) stress-related mental health problems seen in the primary care setting are the same nor can they be treated in a similar fashion.

Table 7: Cost differences, effect differences, and incremental cost-effectiveness ratios from the cost-effectiveness and cost-utility analyses from the ancillary subgroup complete case analysis.

	Sample size		Cost difference (95% CI)	Effect difference (95% CI)	ICER	Distribution in CE-plane			
	MISS	UC				I *	II †	III ‡	IV §
Stress-related mental disorders (SMD)									
Gross sick leave days	57	26	297.64 (-372.42; 1,002.80)	74.00 (14.75; 132.85)	4.02	77%	22%	0%	1%
QALY	56	26	-6157.70 (-12,261.08; 1,229.37)	0.03 (-0.04; 0.09)	-193,892.06	1%	84%	15%	1%
Other mental health problems (MHP)									
Gross sick leave days	28	25	664.17 (-300.39; 1,519.14)	-21.98 (-83.37; 36.45)	-30.22	19%	4%	3%	75%
QALY	26	25	2015.75 (-5,397.10; 100,006.85)	0.01 (-0.08; 0.11)	214,088.31	39%	22%	7%	32%
Somatic problems (SP)									
Gross sick leave days	24	30	-43.40 (-780.81; 812.15)	-4.48 (-49.60; 38.07)	9.68	18%	28%	21%	33%
QALY	21	28	4,707.45 (-3,681.04; 12,291.21)	-0.03 (-0.13; 0.06)	-135,885.50	22%	4%	10%	64%

* Refers to the northeast quadrant of the CE-plane, which indicates that MISS is more effective and more costly than UC.
† Refers to the southeast quadrant of the CE-plane, which indicates that MISS is more effective and less costly than UC .
‡ Refers to the southwest quadrant of the CE-plane, which indicates that MISS is less effective and less costly than UC .
§ Refers to the northwest quadrant of the CE-plane, which indicates that MISS is less effective and more costly than UC .

The negative finding based on the total group, yet positive result for a pre-planned subgroup, may be attributable to the variability in the psychopathology of study population, reflective of the broad inclusion criteria. This suggests that a future clinical trial comparing MISS to UC should be conducted in which individuals with a stress-related mental disorder (SMD) are identified *a priori*, in order to confirm the current finding. A related challenge, however, is that primary care patients typically have an admixture of psychological and somatic symptoms. Current primary care diagnostic or dimensional systems to distinguish between patients with subacute psychopathology that is clearly related to stress (SMD) from those with an admixture of symptoms fall short. Thus, further efforts to improve GP's diagnostic abilities are needed.

The third objective was to investigate the cost offset of the MISS compared to UC in terms of productivity gains. The range of findings from both a societal and company's perspective is reflective of the different assumptions underlying the methods used to estimate the monetary equivalent of productivity changes. The cost offset was also evaluated from a company's perspective as the results based on a societal perspective may not be meaningful [35-37]. Furthermore, companies are key stakeholders in preventing work disability, and decision makers within them can have direct influence on workplace factors that affect health-related productivity [38]. With respect to the FCM and HCA to value productivity changes from a societal perspective, the fact that the offset becomes negative when the number of sick leave days are capped as in the FCM, is indicative of slightly more outliers in the UC group, which have been "adjusted" by the capping process. It should also be noted that the potential offset of any intervention compared to another may be affected by how the friction period is defined, as the duration of the friction period is a dynamic entity, dependent on a given country's unemployment rate.

Methods of estimating productivity loss costs notwithstanding, an investment in MISS may be associated with a positive cost offset in terms of productivity gains from a company's perspective. The actual cost offset for a given company will depend on the socioeconomic context of the company as the context will dictate the relevant investment costs and which assumptions underlying the methods of valuing productivity changes best approach the reality of company. Given that the trend is toward knowledge-based industries, in which work is more often team-based and cognitive in nature, the estimation derived with the inclusion of the median wage multiplier may be the most accurate.

To the authors' current knowledge, this is the first economic evaluation to compare two different approaches by GPs in managing persons with mild stress-related mental health problems. Recently, Brouwers et al. [39] reported on the cost-effectiveness and cost-benefit of an activating intervention by social workers compared to usual care by GPs in persons in a similar group of primary care patients. The results indicated that the intervention by social workers was not more cost-effective than usual care by GPs. There were no significant differences in neither medical consumption nor sick leave duration. Mynors-Wallis et al.[40] found that health care costs associated with a problem-solving treatment for emotional disorders given by community nurses was offset by savings in the cost of sick leave compared to usual care by GPs, with a caveat that such benefit is dependent, again, on the selection of appropriate patients. In a 3-arm pragmatic randomized control trial comparing generic care or problem-solving treatment by community nurses and usual GP care for adults

with anxiety, depression or reaction to life difficulties, Kendrick et al. [41] found that neither nursing care was more cost-effective than usual care by GPs.
Finally, there are two methodological limitations to be addressed. First, the small(er) sample size of complete cases decreases the power to detect relevant differences with regards to skewed cost data [42]. As there were no significant differences between baseline characteristics or symptom severity scores between drop-outs and completers, it is not expected that the cost-effectiveness of MISS compared to UC would be different for drop-outs. Moreover, the findings of the sensitivity analysis with imputed data indicated that the results of the main analyses were fairly robust. Second, work-presenteeism was not included in assessing the functional recovery of workers [3,7,43]. Before and following periods of sick leave, the work performance/productivity of individuals with stress-related mental health problems may be suboptimal [44,45]. Thus, there may be an underestimation of productivity loss, and conversely, an incomplete picture of functional recovery.

Conclusion

While the minimal intervention strategy for workers with stress-related sick leave (MISS) was not associated with a superior clinical or economic impact than usual GP care for a heterogeneous population with stress-related mental health problems, it may be a promising intervention for the subgroup, stress-related mental disorders. Future research should aim to confirm this observation.
Also, the ability to work is an important functional outcome for adults of working age whose productive capacity is (temporarily) impaired for health-related reasons. Further attention to how changes in health-related productivity are conceptualized, measured and valued is needed in order to improve the meaningfulness of future economic evaluations.

Figure legends

Figure 1:
Cost-effectiveness planes representing the uncertainty around the incremental cost-effectiveness ratio for the mean difference in total investment costs divided by the mean difference in gross sick leave days for the total group and subgroups.

Figure 2:
Cost-effectiveness acceptability curves showing the probability that the MISS is cost-effective compared to UC in terms of incremental investment costs and gross sick leave days for the total group and subgroups.

Figure 1:

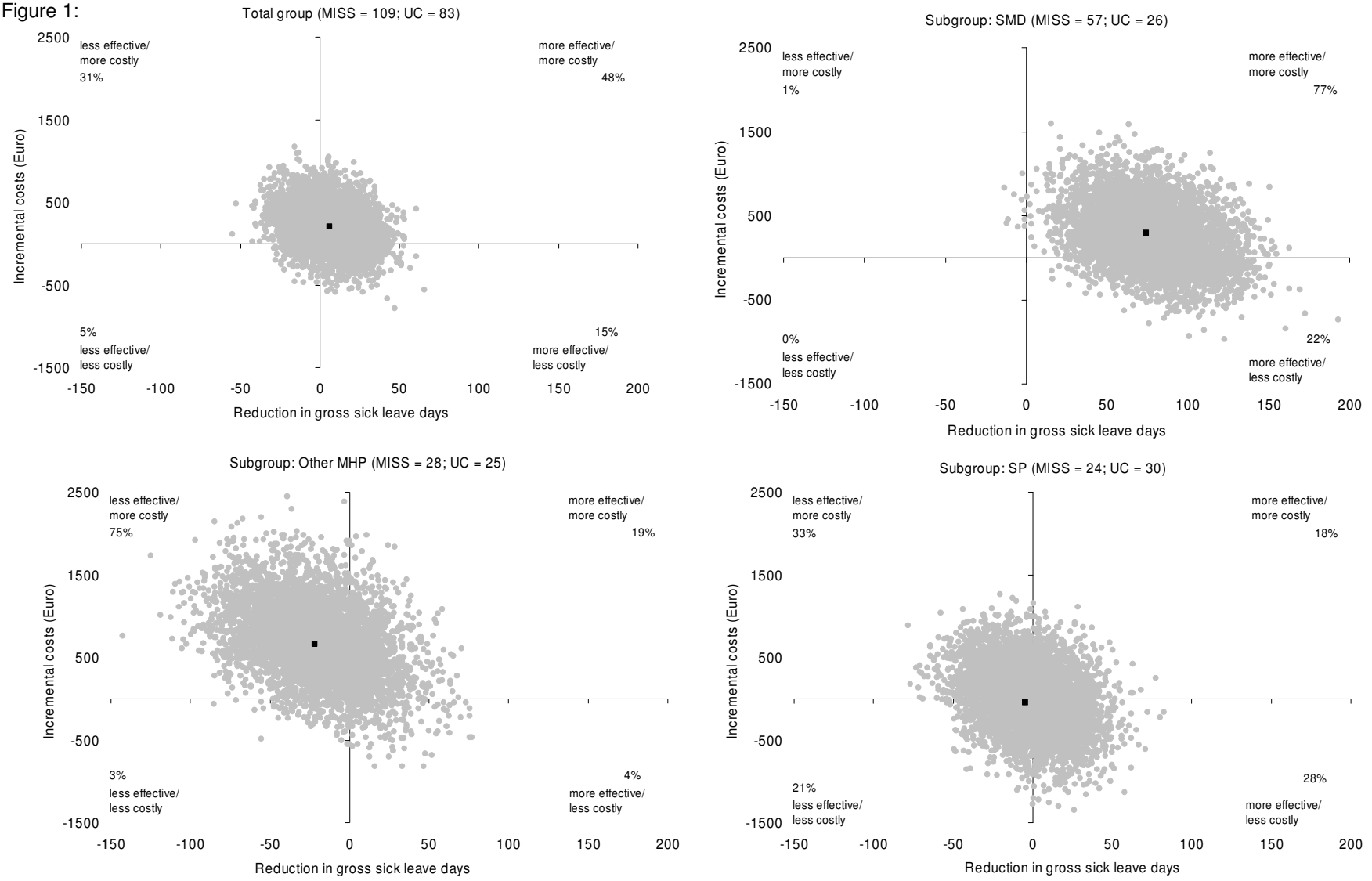
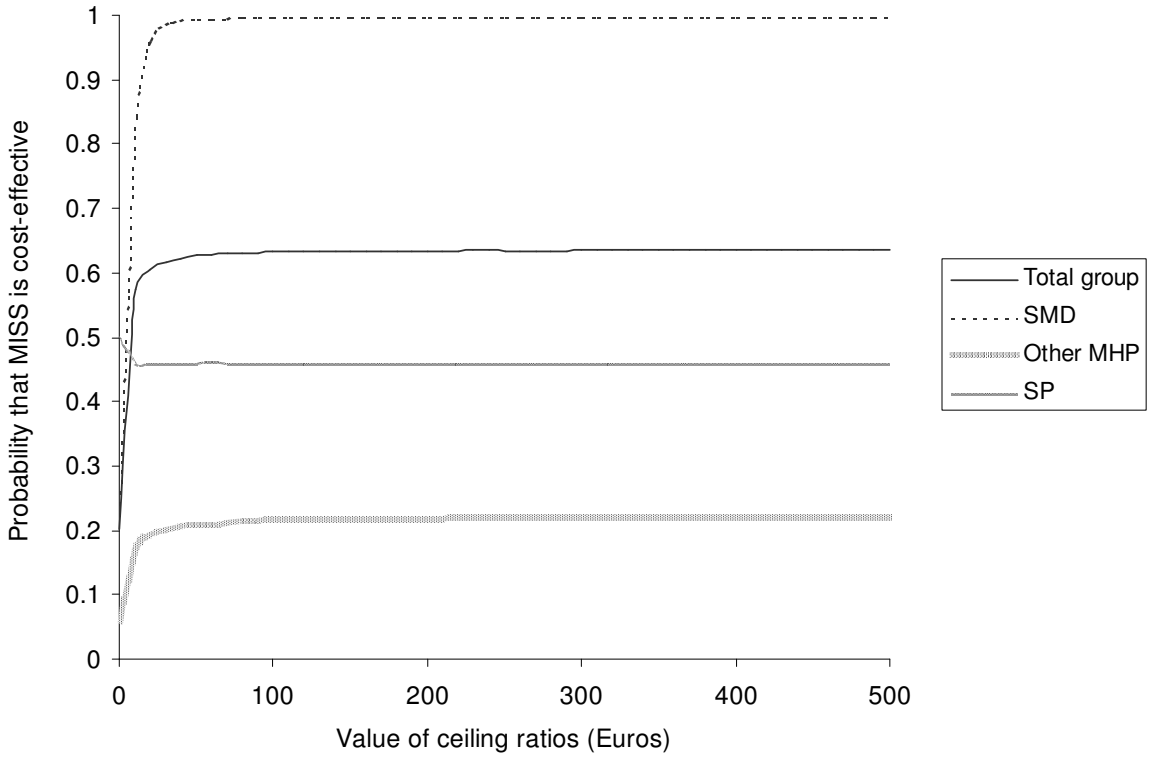

Total group (MISS = 109; UC = 83)
less effective/ more costly 31%
more effective/ more costly 48%
5% less effective/ less costly
15% more effective/ less costly
Incremental costs (Euro)
Reduction in gross sick leave days
Subgroup: SMD (MISS = 57; UC = 26)
less effective/ more costly 1%
more effective/ more costly 77%
0% less effective/ less costly
22% more effective/ less costly
Subgroup: Other MHP (MISS = 28; UC = 25)
less effective/ more costly 75%
more effective/ more costly 19%
3% less effective/ less costly
4% more effective/ less costly
Subgroup: SP (MISS = 24; UC = 30)
less effective/ more costly 33%
more effective/ more costly 18%
21% less effective/ less costly
28% more effective/ less costly

Figure 2:


Probability that MISS is cost-effective
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
100
200
300
400
500
Value of ceiling ratios (Euros)
Total group
SMD
Other MHP
SP

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6

Teaching a minimal intervention for stress-related mental disorders with sick leave (MISS): effects on performance of the general practitioners

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Submitted

Abstract

Background Mental health problems are a major medical and societal burden, associated with reduced quality of life, dysfunctioning and high costs due to sick leave. The worldwide reported prevalence of mental health problems in the working population ranges from 10 –18 %, and in up to 90% of the disability benefits paid because of mental health problems, the initial context or cause is stress- related. We developed a generic Minimal Intervention teaching package to help GPs in the management of Stress-related mental disorders with Sick leave (MISS). The aims of the MISS are to reduce the number of days of sick leave and to prevent chronicity of symptoms in patients with relevant dimensions of psychopathology in which the initial context or cause is clearly related to stress. These aims can be achieved by the assignment of a correct diagnosis, providing information and advice, monitoring the symptoms and –when necessary- referral to more extensive care. We conducted this study alongside a randomised controlled trail assessing the effectiveness in general practice. The aim of the present study was to evaluate the potential differences between the MISS and usual care (UC) in application of treatment-components.

Method 46 GPs joined the study. Twenty-four GPs were randomly assigned to the MISS group, 23 of whom completed the 11-hour MISS training. Information on application of the treatment components was derived from questionnaires filled in by both the GP and patients, and from the electronic medical record of the patient.

Results A psychological diagnosis was more frequently diagnosed by the GPs in the MISS group than by the GPs in the UC group (78.1% versus 67.4%, p=0.020). Furthermore, the GPs in the MISS group more often used a mental health questionnaire (the 4DSQ) (16.1% vs. 1.3%, p=0.000), handed out information leaflets (28.3% vs. 10.8%, p=0.001) and knew how the patients were doing two months after baseline (76.4% vs. 65.7%, p=0.041). The treatment components advice and referral did not show significant differences between MISS and UC.

Conclusion GPs can be trained to apply the MISS intervention on patients with SMDs on sick leave, and also are able to apply the necessary skills for successful treatment in daily practice.

Background

Mental health problems are a major medical and societal burden, associated with reduced quality of life, dysfunctioning and high costs due to sick leave [1-4]. The worldwide reported prevalence of mental health problems in the working population ranges from 10 –18 % [5;6] and in up to 90% of the disability benefits paid because of mental health problems, the initial context or cause is stress- related [1-3;7]. A wide range of symptoms is present, accompanied by a significant amount of psychological distress[8]. These stress states are often sub-acute, but not yet chronic, and are referred to as adjustment disorder (DSM-IV)[9;10], neurasthenia (ICD-10)[11] or 'nervous breakdown'. Since there is a lack of generally accepted criteria for this highly prevalent condition, we refer to it here as Stress-related Mental Disorder (SMD). Subsequent to SMDs, persistent distress contributes to more severe psychopathology and chronic conditions, such as depression and anxiety disorders[12].

GPs are usually the first, and in many cases the only health professionals who are involved in the management of mental health problems[13]. There are general practice guidelines available for the treatment of depression[14] and anxiety[15], but these do not cover stress as a separate aspect of the problem or consider functional recovery as an effect-generator for well-being. The care that is provided for SMD patients on sick leave is very heterogeneous and sub-optimal[16]. We therefore developed a generic Minimal Intervention teaching package to help GPs in the management of Stress-related mental disorders with Sick leave (MISS) and conducted an RCT to assess the effectiveness of the MISS in general practice. The focus was on a reduction in days of sick leave and SMD symptoms. The patients were screened by the research team for elevated levels of distress and sick leave, and the GPs were trained, but not obliged to make use of the training. Although the results showed no overall effects at patient level, our expectation that the patients in the MISS group would return to work more quickly than patients in the UC group was confirmed in ancillary analyses on the sub-group of patients in which the GP had actually diagnosed SMD (HR1.72, p=0.005).

Subsequently, we wanted to find out if there were differences between MISS and Usual Care (UC) in application of treatment-components.

Methods

The present study is a cluster-randomised controlled effectiveness trial in which GPs were randomised to an intervention group, which was trained to deliver a minimal intervention for stress-related mental disorders, or to a control group that delivered care as usual. Distressed patients on sick leave visiting the practices of both GP groups were screened, included and followed-up for 1 year. The Medical Ethics Committee of the VU University Medical Centre approved the study protocol and procedures.

Objective

The aim of this study was to assess the performance of the GPs on the MISS- treatment components.

We hypothesised that the GPs in the intervention group could be trained to diagnose a psychosocial diagnosis, and would apply the learned skills on information, advice, monitoring and referral in daily practice. The performance of the UC group is considered to be the standard of current practice on the different components. Differences between MISS and UC are considered to be an effect of our training.

GPs: randomisation and training sessions

The GPs were randomised to the MISS intervention group or to a control group providing usual care. In order for the MISS to be helpful in routine general practice consultations, the necessary set of skills was clearly defined and taught to the GPs in a short training course. Case-management principles[17;18] were used in the design of the intervention. Over a period of 6-10 weeks, the MISS training comprised two sessions of 3.5 hours and 2 regular follow-up sessions of 2 hours (total 11 hours). The tutors during the training were the GP who developed the intervention (BT), and an occupational physician. During the training, the GPs were instructed to use specific methods of communication to help the patient, within 3 consultations on a time-contingent course, to achieve functional recovery. The MISS takes into account the time-constraints under which a GP works, as well as the position of a GP as a generalist who does not have the capacity to apply highly specialized interventions.
Firstly, the GPs were taught to *diagnose an SMD,* preferably during the first consultation. They were taught how to use the Four-Dimensional Symptom Questionnaire (4DSQ)[19], a multidimensional psychopathological indicator to quantify the levels of distress, and to detect symptoms of depression, anxiety and somatization. They were then taught how to use the *information* leaflet, the purpose of which is to help the GPs in promoting the patient's understanding and to emphasize the importance of the patient's active role with regard to successful return to work. Subsequently, they practised giving *advice* on the content of functional rehabilitation. The GPs were taught how to underline the importance of a balance between resting and addressing the problems that caused the SMD and sick leave, and to recommend the patient to contact the occupational physician. Furthermore, the GPs were invited to suggest a home assignment (i.e. writing, brooding), in order to assist the patient to formulate the problems. For the second consultation, after one week, the GPs were taught active *monitoring* to evaluate whether the patient had made efforts to translate the (work)situation into a problem that could be solved. If helpful, further advice was given. For the last consultation, after four weeks, the GPs were taught to monitor whether the patient had begin to focus on problems and solutions, instead of on complaints. If not, the GPs were instructed to consider *referral* to more specialised care because no progress had been made, and the patient was not likely to benefit from more time off work.
Throughout the training, the skills needed for successful treatment were accentuated, and information was given about the content of relevant work-related polices and regulations. The GPs own experiences were discussed and evaluated, and they provided case-histories in order to practise the different parts of the intervention during the training. The GPs in the UC group received no information or advices about the content of the intervention beforehand, but were offered the training at the end of the trial.

Patients: screening and recruitment

After assigning the GPs, and after 7 hours of training had been completed, the research team started screening the patients. This was done to prevent selection bias, since recognition of SMD and other mental health problems by the GPs could be influenced by education in the MISS intervention group. Furthermore, overlap and co-morbidity of SMDs with other common mental disorders was likely to occur in some patients, and these patients may also benefit from the MISS. SMD was defined as elevated levels of self- reported distress, in combination with sick leave. Patients received a screening questionnaire if they

were 20-60 years old and had visited their GP during the previous one or two weeks, according to the electronic medical records (EMR). Only those indicated by the GP as having a very severe psychiatric disorder (mania or psychosis), terminal illness or inadequate command of the Dutch language did not receive a screening questionnaire. Patients were asked only to return the questionnaire if they met the following criteria: 1) a moderately elevated level of distress, according to the 4DSQ and 2) on sick leave from their paid job for no longer than three months[20]. Final recruitment took place in a telephone survey, after the patient had received the relevant information and had given oral informed consent. The patients and interviewers were unaware that two different interventions were being studied. Actual treatment decisions concerning the patients were left to the professional discretion of the GPs, who were informed about a patient's participation after two months. Follow-up of patients, by means of telephone and postal questionnaires took place up to and including 1 year after baseline. The Medical Ethics Committee of the VU University Medical Centre approved the protocol of the study and the procedures.

Outcome measures

The treatment-components were assessed by analysing reports from the patients and the GPs, and data on the patient's EMR. Only data on patients who, subsequent to oral, had given written informed consent were considered. Two months after inclusion, the GPs filled in a questionnaire, partly based on information from the EMR. Because we did not want to reveal specific MISS components to the GPs in the UC group, there were items we did not ask about directly. Therefore, two months after the baseline measurement, the patients were asked about those components of the MISS. At the end of the follow- up we collected information from the EMRs.

To analyse the diagnoses, data from the GPs were divided into three sub-groups: SMDs, other mental health problems, and somatic diagnosis. Use of the 4DSQ was assessed by studying the notes in the EMR, that were collected at the end of the follow-up. The patients were asked whether the GP had handed out information leaflets. For the specific advice directed at functioning, we also analysed data reported by the patients. For monitoring, which was difficult to measure without directly asking the GPs, we analysed reports from the GPs and the patients and the information from the EMR. The number of visits to the GP from the first day of sick leave until three months after sick leave (a time span in which the MISS, if considered, should at least have been applied) was also extracted from the EMRs. Finally, referral was measured by means of the information given by the GP on the questionnaire after two months.

Statistical analysis

All analyses were conducted according to the intention-to-treat principle. For dichotomous or categorical data, proportions were calculated and tested with Chi-square. For numerical data, means were calculated and tested. The differences between MISS and UC were expressed as p-values. First, we assessed whether GPs in the MISS group were more successful than GPs in the UC group in the identification of SMDs and other mental health problems. Second, we evaluated the application of MISS treatment-components and the resulting difference the MISS group and the UC group. Third, outcomes were analysed at sub-group level, since modification of treatment effects was likely to occur when a GP actually diagnosed SMD. All analyses were performed with SPSS 12.0.

Results

Of the 139 GPs who were invited by mail, 46 were able and willing to participate. Twenty-four GPs were randomised to the MISS group, 23 of whom completed the training. Table 1 shows that characteristics of GPs and patients were largely similar. Data on the application of treatment-components, reported by the GPs, were available for 201 patients (88.5%) in the MISS group and 172 patients (83.5%) in the UC group. Missing data were due to the fact that patients had not given written informed consent. Information from the EMRs was available for 180 patients (79.3%) in the MISS group and 153 patients (74.3%) in the UC group. Again only data on patients who had given written informed consent were analysed and some patients were lost to follow-up on their EMRs. Self-reported data was available from 119 patients (52.4%) in the MISS group and 99 patients (48.1%) in the UC group. A number of patients (MISS n=63, 31.0% and UC n=52, 30.4%) indicated that they had not visit their GP during the previous 2,5 months, so questions about providing advice could not be answered by these patients. Some other patients (MISS n=45, 16.6% and UC n=55, 21.5%) were lost to follow-up on the self-reported patient data.

Table 1 Baseline characteristics

General Practitioners		**MISS (n=24)**	**UC (n=22)**
Age mean (SD)		43.3 (7.4)	44.8 (7.1)
Women N (%)		12 (50.0%)	11 (50.0%)
Years of practice mean (SD)		16.5 (7.2)	18.3 (6.5)
Patients		**MISS (N=227)**	**Usual Care (N=206)**
Women N (%)		153 (67)	134 (65)
Mean age (SD)		41.97 (8.8)	39.50 (9.6)
Married or cohabiting N (%)		174 (78)	148 (72)
Level of education N (%)			
	Low	59 (27)	46 (22)
	Intermediate	94 (42)	102 (50)
	High	70 (31)	57 (28)

The GP performances on all treatment-components are presented in Table 2. Both SMDs and other mental health problems were more often diagnosed by the GPs in the MISS group than by GPs in the UC group, with a total of 78.1% versus 67.4% (p=0.020). The GPs in the MISS group also more frequently used the 4DSQ to make a diagnosis (16.1% vs. 1.3% in UC group, p 0.000), particularly in the subgroup SMDs (MISS 25.6% and UC 3.6%, p=0.001).

According to the patients, information leaflets were handed out by the GPs to 28.3% of the patients in the MISS group and 10.8% of the patients in the UC group (p=0.001), again particularly in the subgroup of SMDs (MISS 41.1% and UC 5.4%, p=0.000). With regard to giving advice, GPs in both the MISS and the UC group GPs often discussed the work situation with their patients (74.0% and 74.8%, p=0.865). But giving other advice, on the content of work (MISS 41.7% vs. UC 36.9, p=0.865) or with regard to contacting the occupational physician (MISS 48.8% vs. UC 46.4%, p=0.421), was less common practice.

With regard to the content of monitoring, the GPs in the MISS group indicated that they more often knew how the patient was doing two months after baseline (MISS 76.4% vs. UC 65.7%, p=0.041), but not particularly in the subgroup of SMDs. No differences were found between the two groups with regard to the number of visits (MISS 2.55 vs. UC 2.50, p=0.839), the number of home assignments (MISS 26.2% vs. UC 27.0%, p=0.884), and the number of invitations of GPs for return visits (MISS 11.7% vs. UC 9.2%, p=0.468). Finally, there was no significant difference in the rate of referral to more extensive mental health care between the two groups (MISS 43.4% vs. UC 37.1%, p=0.160). However, referral was more frequent in the MISS group in the case of SMDs (MISS 59.6% and UC 43.8%, p=0.053), while there was a trend for referral in the UC group for other mental health problems (MISS 50.0% and UC 62.0%, 0.198).

Discussion

Our findings confirm that GPs can be trained to apply the MISS successfully, and that they are also able to apply at least some of the crucial skills in daily practice. Both SMDs and other mental health problems were more frequently diagnosed by the GPs in the MISS group than by the GPs in the UC group. GPs in the MISS group more often used the 4DSQ, and handed out information leaflets, particularly in the case of SMDs. They also more often knew how patients were doing two months after baseline, compared with GPs in the UC group. Finally, in the case of SMDs there was a trend for more frequent referral in the MISS group than in the UC group.

Teaching a GP to diagnose an SMD seems to be crucial for the effectiveness of the MISS training. The GPs in the MISS group more often quantified the level of distress, depression and anxiety with the 4DSQ. Differentiating between distress, on the one hand, and depression and anxiety on the other hand, probably brought about better understanding of the nature of these symptoms. Subsequently, it appears that knowledge of specific methods of communication was retained; MISS-trained GPs had a better grip on the course of SMD symptoms, and their actions were more efficient. This is important, because the management of SMDs is in some ways different from the management that is commonly applied to mental health problems (e.g. guidelines for the treatment of depression[21] and anxiety[22]). For example, it is important that GPs are aware that a wait-and-see policy can be of help in the treatment of depression[23;24], while this can have reverse consequences in the treatment of SMDs because the problems that lead to dysfunctioning (e.g. sick leave) need to be challenged, and resting only may provoke long-term sick leave and total withdrawal from employment[25]. Close monitoring was found to be effective in a collaborative care model[26], and may also be one of the key elements of the effectiveness of the MISS. Case-management might be one way in which to improve care[27], but more is needed if an intervention is to achieve change. It must be clearly defined, tailored to a specific setting and target groups, and the GPs must be trained. Finally, GPs must be able to explain the intervention clearly to patients, within the time-constraints of a relatively brief consultation[28]. All these aspects were addressed in the MISS.

There are various factors and potential barriers that may affect the successful implementation of innovations in routine general practice[29]. Consistently, there is always a gap between best practice and actual clinical care[30]. The low application rates found for some components of the MISS are comparable with the results of earlier research[31-35]. GPs are, by definition, generalists who have to divide their limited time over multiple competing

demands. Interactive education, as applied in our study, including discussion of the evidence and feedback on performance, promotes awareness, familiarity and motivation for change[36;37]. In earlier research, GPs did not often discuss the patient's working conditions (28.0%)[38]. In our study, advice was given frequently in both the MISS group and the UC group. This may indicate that the GPs who participated were aware of and familiar with psychological symptoms and sick leave among their patients. Furthermore, both the social and the political context also influence the achievement of changes in patient care[39]. They may also have played a role here, because there is growing awareness that SMDs can be treated successfully, and that long-term sick leave can be prevented if SMDs are diagnosed and treated in an early stage[40].

Evidence of the effects of brief psychosocial interventions applied by GPs is inconclusive. The results of some earlier studies are promising[41-43], while others are negative[44]. On the other hand, a complex and extensive intervention for mental health problems (e.g. cognitive behavioural therapy for patients with chronic fatigue syndrome) showed a lack of efficacy[45]. More evidence is needed before definite conclusions can be drawn about psychosocial intervention applied by the GP.

Some limitations of this study should be mentioned. In our pragmatic trial we allowed considerable variation in the treatment steps. Methodologically, some parts of the intervention were difficult to evaluate. Also, we did not structure observation of the application of MISS components during consulting hours (which for instance can be done by means of a standardised form, and video or audio-taping) because we gave priority to addressing the performances of the GPs and their application of the intervention in daily practice. Furthermore, in addition to the single self-reported GP measurement, we used the EMRs and patient questionnaires to analyse the data. Although these widely reflect the care provided, they were not designed to specifically test the application of treatment components. On the other hand, the use of different data-sources strengthens our findings with regard to the effectiveness of the MISS compared to UC, and we have no reason to suspect biased registrations.

This study also has certain specific strengths, and many elements indicating quality[46] were incorporated. We carried out a randomised controlled trial to test effectiveness of the MISS, and thereby allowed considerable variation in context, diagnosis and treatment. Consequently, the flattering of performances or the over-estimation of application is not likely to have occurred. Instead, this increased the relevance of our results because it reflects daily practice, and not ideal circumstances. Finally, we included a large number of GPs (MISS 24 and UC 22) in our trial, so bias due to variation in performance of the GPs is not likely to have occurred. Moreover, the large number of patients made it possible to analyse at patient sub-group level.

Implications for general practice

We assume that the components that were found to be more effective than UC (diagnosis, use of 4DSQ, handing out information leaflets, monitoring, and more frequent referral in the case of SMD) are the effect generators of the positive results found at patient sub-group level. Clearly, however, there is room for improvement, since the new skills and knowledge gained from the MISS training were not applied to all patients with SMD, and patients with other mental health problems did not benefit from the MISS. However, the difference found between the sub-groups of diagnoses supports a generic approach, which initially aims at the

level of distress. Differentiating between distress (e.g. SMD), on the one hand, and depression and anxiety (e.g. other mental health problems) on the other hand, appears to be crucial for the effectiveness of the MISS compared to UC.
The MISS can be taught to GPs in 11 hours of training, and has the potential to impact beneficially on large numbers of patients in routine practice, given the burden of mental health problems in general practice. To achieve this, in future more attention must be paid to the definition and diagnosis of an SMD, with the distress as a characteristic and return to work as a strategy for generating effect on well-being. Distress underlies more chronic and severe psychopathological states, such as major depression and anxiety disorder, but distress also represents a highly prevalent and relevant condition of SMD. This study supports the hypothesis that the management of this condition can be carried out within the time-constraints of a brief consultation. However, the necessary communication with patients differs from the techniques that are commonly applied for mental health problems. Therefore, training in the use of the MISS components is essential.

Table 2. GPs performances on treatment components. Values are N (%), unless stated otherwise

				Total Group			Subgroup stress-related mental disorders			Subgroup other mental health problems			Subgroup somatic diagnosis		
1	***Diagnosis***	**Source**	**Data available**	**MISS**	**UC**	***p***									
	Psychosocial diagnosis (SMD or other mental health problems)	GP	MISS n= 201 UC n= 172	157 (78.1)	116 (67.4)	*0.020*	**MISS**	**UC**	**p**	**MISS**	**UC**	**p**	**MISS**	**UC**	**p**
	4DSQ use	EMR	MISS n=180 UC n=153	29 (16.1)	2 (1.3)	*0.000*	20 (25.6)	2 (3.6)	*0.001*	7 (13.5)	0 (0.0)	*0.016*	1 2.4)	0 (0.0)	*0.272*
2	***Information***														
	Information leaflets received	Patient	MISS n=119 UC n=99	36 (28.3)	12 (10.8)	*0.001*	23 (41.1)	2 (5.4)	*0.000*	6 (15.4)	5 (13.9)	*0.855*	5 (20.8)	4 (15.4)	*0.616*
3	***Advice***														
	Work situation discussed	Patient	MISS n=119 UC n=99	94 (74.0)	83 (74.8)	*0.865*	46 (82.1)	30 (81.1)	*0.897*	29 (74.4)	31 (86.1)	*0.204*	14 (58.3)	15 (57.7)	*0.963*
	Advice given on the content of work	Patient	MISS n=119 UC n=99	53 (41.7)	41 (36.9)	*0.421*	29 (51.8)	14 (37.8)	*0.187*	14 (35.9)	15 (41.7)	*0.608*	8 (33.3)	7 (26.9)	*0.621*
	Contact with occupational physician discussed	Patient	MISS n=119 UC n=99	61 (48.4)	51 (46.4)	*0.753*	30 (53.6)	20 (54.1)	*0.964*	18 (46.2)	16 (45.7)	*0.970*	9 (37.5)	7 (26.9)	*0.423*
4	***Monitoring***														
	GP evaluation on the course of patient	GP	MISS n= 201 UC n= 172	150 (75.4)	111 (65.7)	0.041	71 (79.8)	48 (73.8)	*0.386*	56 (83.6)	37 (75.5)	*0.281*	23 (53.3)	26 (47.3)	*0.541*
	Number of visits from the day of sick leave + 3 months *Mean (SD)*	EMR	MISS n=180 UC n=153	2.55 (2.12)	2.50 (2.23)	*0.839*	2.60 (1.92)	2.34 (1.84)	*0.435*	3.13 (2.73)	3.20 (2.88)	*0.905*	2.03 (1.59)	1.88 (1.73)	*0.679*
	Home assignment given by the GP	Patient	MISS n=119 UC n=99	33 (26.2)	30 (27.0)	*0.884*	17 (30.4)	12 (32.4)	*0.833*	10 (25.6)	7 (19.4)	*0.522*	5 (20.8)	8 (30.8)	*0.424*
	Invitation for return-visit	EMR	MISS n=180 UC n=153	21 (11.7)	14 (9.2)	*0.468*	15 (19.2)	5 (8.9)	*0.099*	4 (7.7)	4 (10.0)	*0.697*	2 (4.9)	5 (10.2)	*0.347*
5	***Referral***														
	Referral to more extensive mental health care	GP	MISS n= 201 UC n= 172	86 (43.4)	63 (37.1)	*0.160*	53 (59.6)	28 (43.8)	*0.053*	33 (50.0)	31 (62.0)	*0.198*	0 (0.0)	4 (7.1)	*0.074*

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7

Test-retest reliability of the Primary Care Evaluation of Mental Disorders (PRIME-MD): limitations in the current system of diagnosing mental disorders in primary care

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Submitted

Abstract

Background The Primary Care Evaluation of Mental Disorders (PRIME-MD) can be seen as characteristic for the process of successive refinements of criteria and structured interview techniques for diagnosing psychiatric disorders in primary care. It is one of the most widely used instruments, but there is no evidence to support its test-retest reliability.

Method With one- week intervals between interviews, a test-retest study of the PRIME-MD was conducted in a general practice population of one hundred distressed patients (20-60 years old) who were on sick leave.

Results Almost everyone (89%) received one or more diagnoses at both measurements, and there was fair total agreement (κ .27). The best agreement was found for more severe threshold disorders (major depressive disorder [κ .58], dysthymia [κ .57], and generalised anxiety disorder [κ .59]), while agreement for the sub-threshold disorders was not satisfactory (anxiety disorder not otherwise specified [NOS] [κ .30], minor depressive disorder [κ -.03], and somatoform disorder NOS [κ .11]).

Conclusion The PRIME-MD is one of the few instruments in primary care that actually diagnoses specific mental disorders according to the DSM criteria. However, its test-retest reliability was not satisfactory for the sub-threshold disorders. Mental disorders, as seen in primary care, encompass important specific symptoms and clinical syndromes that vary in duration and severity over time, but they also encompass an admixture of somatic and psychological symptoms that do not match current diagnostic systems. This probably contributes to the failure to adequately classify sub-threshold disorders with the PRIME-MD. Diagnostic criteria in psychiatry need to be operationalised for use in primary care and require further evaluation.

Background

The historically poor reliability of the diagnosis of mental disorders has been the basis for the development and successive refinements of diagnostic criteria[1;2] and structured interview techniques[3]. In clinical practice, the availability of symptom-based criteria has been shown to increase diagnostic agreement[4] and to facilitate communication among mental health professionals[5]. Furthermore, the classification of patients according to a symptom profile can support a prognosis and demonstrate changes in that profile over time. At the moment, the use of structured interviews for mental disorders is the standard in research settings[2], because these procedures signify consistency[6]. However, shortcomings in the diagnostic criteria for to the categorisation of mental disorders in primary care are well known[7-10]. For instance, the dimensional symptom severity gradient should also be considered[11].

In primary care there are some obstacles that limit the willingness of general practitioners (GPs) to accept and implement extended structured interviews[12-14]. For instance, the symptoms must be clarified in a limited amount of time. Another problem is that many instruments fail to take into account the elusive and multidimensional nature of mental disorders, which is typical in primary care patients. To overcome these obstacles, and also to clear up uncertainty about which questions are suitable to assess the diagnostic criteria, the Primary Care Evaluation of Mental Disorders (PRIME-MD)[15] was developed. The PRIME-MD was the first instrument for use in primary care to diagnose specific mental disorders, based on criteria from the diagnostic and statistical manual of mental disorders (DSM-III-R[16] and DSM-IV[17]), and it is still one of the most widely used instruments in clinical research[18]. The PRIME-MD has proven to be feasible and effective in achieving higher rates of detection for the most common mental disorders in primary care[19-21].

However, the issue of its reliability continues to be of foremost importance[22] and there is no evidence to support the test-retest reliability of the PRIME-MD. In the leading PRIME-MD 1000 study, Spitzer et al. found modest inter-rater reliability between the PRIME-MD diagnoses made by GPs and those made by mental health professionals, and it was particularly difficult to achieve high agreement for sub-threshold disorders[15]. Consistency of measurement is a necessity, but is not sufficient proof of the accuracy of any test. Test-retest reliability indicates whether or not a test (e.g. the PRIME-MD) is able to produce the same result on two different occasions under similar conditions, with the assumption that the measured attribute (e.g. symptoms leading to a diagnosis) has remained unchanged[23]. The present study was conducted to determine the test-retest reliability of the PRIME-MD.

Methods

PRIME-MD

The PRIME-MD is based on a two-stage system, in which the patient first completes a 26-item self-administered patient questionnaire (PQ) that screens for the following five most common mental disorders in primary care: mood disorders, anxiety disorders, alcohol consumption, somatoform disorders, and eating disorders. The PQ serves as an initial symptom-screening, and the response categories are dichotomous (yes/ no). Positive answers on this questionnaire trigger the modules of a decision scheme[15]. In the Dutch version of the PRIME-MD[24] 16 possible diagnoses can be made, 8 of which are specific DSM Axis I threshold diagnoses: major depressive disorder, partial remission or recurrence of major depressive disorder, dysthymia, panic disorder, generalised anxiety disorder, bulimia

non-purging type, bulimia purging type, and multi-somatoform disorder. Five of the diagnoses are sub-threshold diagnoses: minor depressive disorder, anxiety disorder not otherwise specified (NOS), probable alcohol abuse or dependence, binge eating disorder, and somatoform disorder NOS. Furthermore, there are 3 diagnosis of rule-out (R/O) disorders: R/O bipolar disorder, R/O depressive disorder and R/O anxiety disorder[24]. With regard to the rule-out disorders, we only studied R/O bipolar disorder, because our independent interviewers did not have accurate information to confirm R/O depressive or anxiety disorder due to physical disorder, medication or other drugs. The original version of the PRIME-MD was based on the DSM-III-R[16]; the Dutch PRIME-MD[24] is based on the DSM-IV[17].

Patients

The data were collected within the framework of a larger study[25] for which the design, protocol and procedures were approved by the Medical Ethics Committee of the VU University Medical Centre. To estimate the reliability of the PRIME-MD, a consecutive sample of primary care patients (20-60 years of age) who consulted the participating GPs, and who had been confirmed by the by the research team as being on sick leave and being distressed, were included in the study. The screening questionnaire included 3 questions from the Four-Dimensional Symptom Questionnaire (4DSQ)[26] distress scale and one question on sickness absenteeism (see Box 1). Only those patients who, according to the GP had a mania, psychosis or terminal illness, or had inadequate command of the Dutch language, did not receive a screening questionnaire.

Box 1 Screening questionnaire

	No	Sometimes	Regularly or often
1. During the past week, did you suffer from worry?	0	1	2
2. During the past week, did you suffer from listlessness?	0	1	2
3. During the past week, did you feel tense?	0	1	2
4. Total score 4 or higher?		Yes	No
5. Do you currently have a paid job?		Yes	No
6. Are you currently on sick leave for a period no longer than three months?		Yes	No

The patients were asked only to return the questionnaire if they answered three times “yes” and were willing to participate in the study.

Table 1 Baseline characteristics (N=100)

Age		**Mean (SD)**	**Range**
Male	N=32	42.0 (9.1)	20-56
Female	N=68	39.7 (9.2)	21-58
Total	**N=100**	**40.4 (9.2)**	**20-58**

Level of education	**Low**	**Medium**	**High**
Male	7	15	10
Female	16	33	19
Total	**23**	**48**	**29**

Marital status	**Single/ divorced**	**Married/ cohabiting**
Male	14	18
Female	32	36
Total	**46**	**54**

In the period from June to September 2004, 135 consecutive patients were included in the study. Data on these distressed patients, who were on sick leave, were collected by trained interviewers (n=7) in a computerised PRIME-MD telephone interview, with a retest interview after one week, if feasible by the same interviewer.
Fourteen of the 135 patients who completed the first questionnaire dropped out of the study before the retest interview. Twenty-one of them were not available for a retest (due to holiday season we were unable to contact the patients in time). Thus, data on 100 patients could be included in the test-retest analyses.

Analyses

The prevalence rates for each diagnostic category and the percentage of agreement (number of patients in the same category both times, positive or negative) were calculated. We computed kappa, which summarises the total agreement between the two measurements beyond what could be expected by chance[27]. A kappa higher than .80 was considered as 'very good', higher than .60 as 'good', kappa's between .41 and .60 were considered as 'moderate'. A kappa between .21 and .40 was considered as 'fair', and scores kappa's below .20 were considered as 'poor'[27]. All analyses were performed in SPSS 12.0.

Results

The patient characteristics, which all had a normal distribution, are presented in Table 1. The mean age of the patients was 40.4 years (SD 9.2), and 68% were female. In 89 out of 100 patients, the same interviewer performed both test and retest. The mean number of days between the two assessments was 7.13 (SD 1.46).

Table 2. Prevalence and agreement between the two measurements for PQ screen (N=100)

PRIME-MD MODULE	Frequency T0	T1	T0 + T1	Raw agreement	Kappa	95% CI
Mood	87	77	74	84	.47	.25 - .68
Anxiety	94	85	83	87	.32	.05 - .59
Alcohol	24	23	18	89	.69	.53 - .86
Eating	32	31	24	85	.65	.49 - .81
Somatoform	93	84	83	89	.47	.21 - .73

Table 2 presents the results of the PQ as a screener for identifying which modules should be administered. Many patients (77- 94%) were entered the mood, anxiety and somatoform modules. This resulted in kappa values ranging from fair to moderate (κ .32 - κ .47). The prevalence of patients entering the alcohol and eating module was lower (23-32%), and showed good agreement (κ .69 & κ .65). In all modules there was agreement of at least 84%.
Table 3 shows the results of diagnoses based on the PRIME-MD. Almost everyone (89%) received one or more diagnoses in both assessments, (97% test and 90% retest). There was fair total agreement between the two measurements (κ .27).
The diagnosis "any mood disorder" had high prevalence rates (84% and 72%), and agreement between the two assessments was moderate (κ .49). Within any mood disorder, major depressive disorder and dysthymia showed the highest total agreement (κ .58 and κ .57). Major depressive disorder was diagnosed most frequently; in 64% and 58% of the patients, and agreement was fair for partial remission or recurrence of major depressive disorder (κ .30) and R/O bipolar disorder (κ .39). For the diagnosis of minor depressive

Table 3. Prevalence and agreement between the two measurements for diagnoses (N=100)

Disorder:	Frequency			Raw agreement	Kappa	95% CI[1]
	T0	T1	T0 + T1			
Any psychiatric disorder	97	90	89	91	.27	-.05 - .60
Any mood disorder	**84**	**72**	**69**	**82**	**.49**	**.29 - .68**
Minor depressive disorder	2	5	0	93	-.03	-.06 - .00
Major depressive disorder	64	58	51	80	.58	.42 - .74
Partial remission or recurrence of major depressive disorder	17	9	5	84	.30	.05 - .55
Dysthymia	29	24	18	83	.57	.38 - .75
R/O bipolar disorder	2	3	1	97	.39	-.17 - .94
Any anxiety disorder	**55**	**42**	**36**	**75**	**.51**	**.35 - .67**
Panic disorder	2	5	1	95	.27	-.18 - .71
Anxiety disorder NOS	23	21	10	76	.30	.08 - .52
Generalised anxiety disorder	32	20	18	84	.59	.42 - .76
Probable alcohol abuse/ dependence	**10**	**5**	**5**	**95**	**.64**	**.36 - .93**
Any eating disorder	**4**	**4**	**3**	**98**	**.74**	**.39 - 1.00**
Bulimia nervosa, 'purging' type	0	0	0	100	-	-
Bulimia nervosa, 'nonpurging' type	2	2	2	100	1.00	1.00 - 1.00
Binge eating disorder	2	2	1	98	.49	-0.12 - 1.00
Any somatoform disorder	**31**	**29**	**16**	**72**	**.33**	**-.14 - .53**
Multi-somatoform disorder	20	13	8	83	.39	.15 - .62
Somatoform disorder NOS	11	16	3	79	.11	-.12 - .33

[1] 95% Confidence Interval (CI)= Kappa (K) +/- 1.96 x Standard Error (SE)

disorder no agreement was found (κ -.03); very few patients (2-5%) were diagnosed with this disorder, and none of them received this diagnosis at both test and retest. In 55 versus 42 patients, "any anxiety disorder" was diagnosed with the PRIME-MD, and agreement was moderate (κ .51). Within any anxiety disorder, generalised anxiety disorder had the highest total agreement between the two measurements (κ .59), and was diagnosed twice in 18 patients. Agreement for the less common panic disorder (2 vs. 5 patients, positive agreement on one) was fair (κ .27), and for the sub-threshold diagnosis anxiety disorder NOS, agreement was also fair (κ .30). Probable alcohol abuse or dependence also showed good total agreement (κ .65), and the diagnosis was not very common (5-10%). Good agreement (κ .74) and low prevalence (4%) was found for the diagnosis "any eating disorder". None of the patients had Bulimia nervosa, 'purging' type, but 2 patients had the 'non-purging type' (κ 1.0). Binge eating disorder was diagnosed in 2 patients, and there was agreement on one (κ .49). In 31 versus 29 patients "any somatoform disorder" was diagnosed, and there was positive agreement on 11 patients (κ .33). Multi-somatoform disorder was diagnosed most frequently, and positive agreement was found in 8 patients (κ .39). No agreement was found for sub-threshold somatoform disorder NOS (κ .11).

Discussion

Summary of main findings

In this PRIME-MD test-retest reliability study, there was fair total agreement between the two measurements (κ .27). The best agreement was found for more severe threshold disorders (major depressive disorder [κ .58], dysthymia [κ .57], and generalised anxiety disorder [κ

.59]), while agreement for the sub-threshold disorders was not satisfactory (anxiety disorder NOS [κ 0.30], minor depressive disorder [κ -.03], somatoform disorder NOS [κ .11]). Notably, in our primary care sample, threshold disorders were diagnosed more frequently than sub-threshold disorders.

Comparison with previous research

As far as we know, this is the first study in which the test-retest reliability of the PRIME-MD has been assessed. Comparison of our results with results on the other aspect of reliability, i.e. inter-rater reliability, which was investigated in the leading publication on the PRIME-MD, was possible for 12 disorder categories. For 10 out of 12 comparative diagnoses the same level of agreement was found in our study and in the PRIME-MD 1000 study. Different agreement values were found for "any psychiatric disorder" (κ .27 in our study, and κ .71 in the PRIME-MD 1000 study) and "panic disorder" (κ .27 in our study, and κ .60 in the PRIME-MD 1000 study). For most threshold disorders there was moderate or (close to) good agreement in both studies. This applies to major depressive disorder, dysthymia, generalised anxiety disorder and bulimia nervosa. As far as the sub-threshold disorders are concerned, only probable alcohol abuse or dependence showed good agreement in both studies; for sub-threshold anxiety disorder NOS and minor depressive disorder there was fair agreement in both studies. For binge eating disorder and somatoform disorder NOS, which were only analysed in our study, there was moderate and fair agreement.

Methodological considerations

Test-rest reliability is determined by many factors. For example, it is dependent on the context in which it was produced [2], the nature of the questions asked, and the conditions in which the interview was held. In our study, all the questions were structured and computer-directed, on the basis of dichotomous answers, and almost all retests were performed by the same interviewer. The rationale for a one-week interval between test and retest in our study was the minimisation of patient changes that could contaminate the results; clinically important changes were not expected to occur within one week. However, test-retest reliability may be affected by the patient remembering and repeating earlier responses, or by a patient's tendency to avoid repetitiveness, thereby offering new information. Furthermore, attenuation, e.g. the tendency of patients to report less symptomatology on successive interviews, may affect test-retest reliability. Our retest took place after one week, and all diagnoses were made less frequently in the retest (see Table 3).

The prevalence, range and complexity of the disorders under study can also play a role in test-retest reliability. The PRIME-MD can be used for patients with suspected mental disorders[15], such as our sample of patients. However, the difficulty here is that the estimate of the kappa statistic depends on the prevalence[27], and in our sample of patients almost everyone (89%) received a psychiatric diagnosis, which may have resulted in an under-estimation of the actual level of agreement. In contrast, the prevalence rate of any psychiatric disorder was much lower in the PRIME-MD 1000 study, e.g. 26% in a sample from the general population, and there was good inter-rater agreement for "any psychiatric disorder". Because of our pre-selection, an immediate comparison of the results of the two samples must be interpreted with some caution. Clearly, in our sample at least some symptoms of distress were already present, so the group was possibly too homogeneous for distinguishing between diagnoses with the PRIME-MD. Yet, an important aspect of diagnostic criteria is

also to distinguish between homogeneous groups with respect to both prevention and treatment response[28]. Adequately differentiating patients with mild symptoms (e.g. sub-threshold disorders) from those who will benefit from specialised treatment (e.g. threshold disorders) and those who do not need treatment (e.g. no disorder) is important, because there is a gradient in adverse consequences associated with the severity of symptoms[29]. Adequate differentiation may be feasible if there is a second confirmation after a few weeks, or a check on the severity of the symptoms.

Generalisability of our findings into clinical practice

In primary care, a wide clinical variation can be expected in the accuracy of diagnoses; e.g. many patients find it difficult to acknowledge mental symptoms, a substantial number of mental problems in primary care are self-limiting, and there is (somatic) co-morbidity. None of these topics are addressed explicitly in the PRIME-MD. Therefore, a structured telephone assessment, made by trained interviewers, cannot replace a face-to-face interview with a GP, who is likely to take several relevant factors into account that cannot be addressed in a structural interview such as the PRIME-MD. This may result in an underestimation of the actual level of agreement. Moreover, several factors that play a role in diagnosing mental disorders were not taken into consideration in our study, because the interviewers did not have the necessary information to assess them, among which the R/O depressive and anxiety disorders, which are actually a part of the PRIME-MD. Yet, it is not likely that this influenced our findings with regard to test-retest agreement. In conclusion, these factors should be taken into account, because of their implications for the generalisation of our findings to clinical practice. The reliability estimates we found are representative for research settings with trained interviewers, but should be applied with some caution in clinical practice. On the basis of the literature and previous experience, we expected more cases to be mild, and also that there would be more diagnosis of a sub-threshold disorder in our sample of distressed patients[30-32]. Yet, it appears that most of the selected patients had a threshold diagnosis on the PRIME-MD. The rates of co-morbidity also seem to be unlikely high. It is argued that the psychological distress that often occurs in primary care patients cannot be defined according to criteria-based diagnostic categories but rather in terms of dimensions and severity of symptoms[33-35]. In our study, every patient had at least some non-specific symptoms that may indicate the presence of a mental disorder, and this made it more difficult to distinguish between threshold, sub-threshold and non-cases. The PRIME-MD tends to diagnose most elevated levels of distress as threshold disorders, rather than sub-threshold disorders. This study provides support for considering the severity gradient of symptoms before assigning a diagnosis in primary care.

Conclusion

In this PRIME-MD test-retest reliability study, the best agreement was found for the more severe threshold disorders, while agreement for the sub-threshold disorders was not satisfactory. Based on the results of several studies, it can be concluded that the PRIME-MD has its value in the feasible and effective time-efficient diagnosis of threshold mental disorders for both clinical and research purposes. The ability of GPs to assess mental health problems varies widely, and this may improve substantially if they make more use of a diagnostic tool such as the PRIME-MD. The DSM criteria are widely accepted, and the PRIME-MD is one of the few instruments in primary care that actually diagnoses specific

mental disorders according to the DSM criteria. But then again, test-retest reliability of the PRIME-MD was not satisfactory for the sub-threshold disorders, and the PRIME MD is overly inclusive for threshold disorders. There clearly are some limitations in the current diagnostic process, and as was already stated by Wittchen, Üstün and Kessler[36], the most appropriate way forward may be to recognize that standardised interviews are necessary, and to be sensitive to the fact that these interviews are not completely perfect. Mental disorders, as seen in primary care, encompass important specific symptoms and clinical syndromes that vary in duration and severity over time, but they also encompass an admixture of somatic and psychological symptoms that do not match current diagnostic systems. This probably contributes to the failure to adequately classify sub-threshold disorders with the PRIME-MD. Diagnostic criteria in psychiatry need to be operationalised for use in primary care and require further evaluation. Dimensional models can offer information that is additional to the categorical diagnosis, but there are still no widely accepted dimensional models and there is a clear need for their usefulness to be compared with that of accepted criteria for the diagnosis of mental disorders in primary care.

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8

General discussion

In this chapter some important issues regarding the design and the results will be discussed. Our research provides us with some answers but creates even more questions. The effect of our minimal intervention for stress-related mental disorders at patient level was less than expected. Results showed no evidence that the MISS is superior to UC on the total group level. Subgroup analyses showed effectiveness and cost-effectiveness of MISS over UC on days of sick leave for the patients that actually were diagnosed by their GP as having a SMD. At the process level, there were improvements on diagnosing psychosocial complaints.
In order to strengthen the body of evidence for (in)effectiveness of the MISS, some considerations covering the foregoing chapters will be discussed. First, the realization of our trial in the general practice setting and key methodological issues will be dealt with. Next, critical factors within the patient population under study, our intervention (the MISS) and the role of GPs will be considered briefly. Finally, the inferences of our research will be explored in terms of overall evidence, recommendations for further research and implications for general practice.

Realization of our trial in the general practice setting

At the start of our study, the perceived relevance on the subject of SMDs and the prevention of long term sick leave was high on the agenda of government policy and the Dutch College of GPs. Nevertheless, we paid ample attention to successful recruitment, because failure to recruit enough GPs and patients frequently threatens the progress of research projects in general practice[1;2]. Attention for our research project was drawn with the help of leading GPs within the network of the Department of General Practice of VU University Medical Center. Receiving the MISS-training was one of the appealing factors for participation in our trail, but some of the GPs indicated that they had a lack of time to take part in the training. We planned to recruit 40 GPs, a total of 46 wanted to participate. We wanted to minimize the research burden for the GP and thus decided to screen the patients ourselves. The GPs did not have to be alert during consultations; the patients were informed by mail. As a result of our screening procedure, the actual number of patients recruited exceeded the pre-planned number (433 vs. 415). We had simple inclusion procedures, and only recruited incident cases. In doing so, we aimed to select patients with SMDs on sick leave for no longer than three months. Beforehand, we thought overlap with depressive disorder and anxiety disorder would be some 25%. We choose this way of screening because 1) no other short and simple inclusion procedure, which is crucial for successful screening of patients, was available and 2) we considered that primary care patients having a variability of psychopathology might also benefit from our intervention.

Methodological issues

In chapter 4-6, some strengths and limitations of our RCT were already discussed at length. In short, clear strengths of this study include the procedures for cluster randomization, in which primary care practitioners were randomized, rather than patients. This process ensures that only patients assigned to the intervention arm received the benefits of the intervention, and “contamination” between intervention and control groups was avoidable. Patients were kept unaware that two interventions were being compared, which also has the advantage of preventing selective withdrawal from the study[3]. This may bring about ethical concerns[4], but we decided that the benefits outweighed the adverse consequences. The medical ethics committee of the VU University Medical Centre approved our design.

The main methodological comment on our study concerns the timing of the diagnosis and measurement of the target condition, SMDs, during the intervention instead of at baseline. One can argue that this approach may have been biased, and that the correct way to handle the issue of subgroups would be to assess the disorders in question in the baseline assessment, not in a follow-up assessment based on GP assessment that could be confounded by training in the MISS. Indeed, the proportion of patients described by the GP as having a psychosocial disorder is higher in the MISS group than in the control group. This can be seen as evidence that the MISS sensitised GPs to this diagnosis, making it invalid to compare patients with this diagnosis across the treatment and control groups. This is a key issue, because our secondary analysis shows that the MISS worked among the subgroup of patients diagnosed with SMD.

Now we will explore our choices with regard to the subgroup analysis step by step. At baseline, we measured severity of complaints with the Four Dimensional Symptom Questionnaire (4DSQ[5]), and we used the Primary Care Evaluation of Mental Disorders (PRIME-MD[6]) because it is one of the few instruments in primary care that actually diagnoses specific mental disorders according to the DSM-IV criteria[7]. However, we tested the PRIME-MD's reliability, and it was not satisfactory for the sub-threshold disorders (i.e. minor depression, anxiety nos). In our sample of patients, almost everyone (89%) received a psychiatric diagnosis with the PRIME-MD. The prevalence, range and complexity of the disorder under study probably played a role[8]. The latent distress, present in our group of patients, may have caused the failure in distinguishing between diagnoses at baseline with the PRIME-MD. So, unfortunately, as was expected with the PRIME-MD, we could not separate those patients with depressive disorder or anxiety disorder at baseline in a reliable way from those with relevant dimensions of psychopathology which are sub-acute, but not yet chronic, and clearly related to stress (e.g. SMDs). Furthermore, we choose to take the diagnoses from the Electronic Medical Record (EMR) of the GPs, because next to important specific symptoms and clinical syndromes (4DSQ, PRIME-MD) that vary in duration and severity over time, we also had to take into account that primary care patients typically have an admixture of somatic and psychological symptoms[9;10]. Since we failed in reliably determining subgroups of patients at baseline by using PRIME-MD scores, the pre-planned subgroups were determined by means of diagnoses stated by the GP, and corrected in the analyses for severity of complaints on the 4DSQ. To collect the data needed on diagnosis, two months after the baseline assessment the GPs in both groups were asked to fill in a structured questionnaire on the care provided and any diagnoses or working hypotheses in the past three months according to their electronic medical record (EMR). We had access to the EMR, so we could confirm that the diagnoses filled in by the GP was alike those stated in their EMR. Furthermore, the GPs did not know at once which patients entered our study. They were informed after a month. So a considerable amount of information on diagnoses or working hypotheses from the EMR was filled out before the GP even knew the patient was involved in our study. In no case we informed the GPs about the patient's score levels on the 4DSQ. However, the diagnosis of a SMD was the first out of five steps in the training, so in fact the intervention was likely to sensitise GPs to this diagnosis. And indeed, the proportion of patients described by the GPs as having psychosocial problems is higher in the intervention group. It seems logical to expect that this result is biased. It is likely that the SMD patients in the MISS group were significantly less severely affected than the SMD patients in the UC group. So, to make the subgroup comparison on diagnosis valid, we took

baseline levels in severity of complaints (distress, depression, anxiety and somatization) into account, thereby controlling for flaws due to more sensitive GPs from the MISS group. The SMD-patients in the MISS group actually turned out to have somewhat higher baseline levels of symptoms than the SMD-patients in the UC group. We conclude that our approach on the subgroup analysis was not biased. Nevertheless the findings must be interpreted with caution.

The patients under study

All patients who entered our study had at least some symptoms of stress-related mental disorder. According to the GP, a diagnosis of SMD was most frequent (MISS 45%, UC 39%), followed by other mental health problems (MISS 33%, UC 29%) and somatic problems (MISS 22%, UC 33%). The symptoms decreased significantly over time similarly in both groups, although severity still was considerable at the end of follow-up. A substantial part of the patients at the end of follow-up still scored above the threshold on symptoms of distress (MISS 44.9%, UC 39.6%), depression (MISS 24.0%, UC 28.8%), anxiety (MISS 13.8%, UC 12.9%) and somatization (MISS 30.5%, UC 33.6%). The threshold was set at moderate elevation of scores. Therefore, scores above threshold did not necessarily indicate a depressive or anxiety disorder. Nevertheless, some patients may have had conditions that were of a more chronic nature and needed more extensive care.

Early and reliable identification of patients at risk for poor outcome should be considered. In chapter 2, we brought up the importance of the concepts of coping and demoralization in the diagnosis and treatment of SMDs. It was argued that approach coping instead of avoidant coping was the way forward. We did measure problem focused coping and avoidant coping with the Ways of Coping Questionnaire[11], but exploratory analyses showed only about 10% of the patients used either one of these styles. There were no differences in coping style between MISS and UC, either at baseline or at follow-up. Unfortunately, these two scales were the only coping styles measured. Furthermore, it was argued that demoralization is an important link between common mental disorders and sick leave, and may be viewed as a combination of distress and subjective incomp0etence, and is distinguishable from depression by the absence of anhedonia. However, studying the empirical framework, demoralization as a latent structure of symptoms[12;13] or demoralization captured within the dimension of distress[14], exceeded the scope of our trial. As a result, we cannot make definitive statements concerning some critical factors within patients, like coping and demoralization which play a role in the element of monitoring the patient.

The intervention

The intervention was developed on the base of three consultations for each patient with SMD. One may argue that our MISS lacked intensity to guarantee adequate assessment and treatment of symptoms of SMD. Results show that patients did not visit their GP exactly three times. The number of visits to GP consulting hours from the first day of sick leave up to three months was 2.55 for the total MISS group and 2.50 for the total UC group. Possibly the GPs may not have had the ability to apply what they learnt in the training program within less than three consultations. But then again, during the training sessions GPs were advised to subdivide their intervention in three consultations, but this was not taught as a necessary condition. Instead, if the diagnosis (of a SMD) was clear at first consultation and the patients already showed efforts to deal with problems and solutions, instead of solely focus on the

symptoms, the MISS was suggested to be done in 2 consultations. Moreover, the GP was advised, but not obliged, to use the MISS or ask the patients for a return visit. In a comparable study in occupational health care effectiveness of the intervention was proven. In that study, the OP had to plan four or five consults with a total length of at least 90 minutes[15]. One may be inclined to conclude that more intensive interventions are more effective[16], but then the question of feasibility of a more intensive intervention in the time schedule of general practice raises.

Next, a possible explanation for the lack of effect is that the contrast between MISS and UC was too minimal. The GPs who decided to participate might have been especially interested in the diagnosis and treatment of SMDs, although it is a topic that every GP takes notice of in daily practice. The content of the control treatment was not standardised, since no guidelines were available, but we did have information about the application of MISS-treatment components by the GPs in the UC group, and we did have some information available from another study[17] which evaluated the frequency and content of contact between workers who were sick-listed and their GP. In our study, a difference in favour of MISS was seen on several treatment components (diagnosis, information and monitoring). In the case of giving advice, both the MISS and UC GPs often discussed the work situation with the patient. Advice on the content of work were given to 41.7% (MISS) and 36.9% (UC) of the patients, and discussing contact with the OP was done according to 48.4% (MISS) and 46.6% (UC) of the patients. Anema et al[17] report that sick-listed workers discussed working conditions with the GP less frequently (28.0%), and according to his study a work related intervention was never done by the GP. The numbers found in our study on giving advice on the content of work is high compared to those reported by Anema et al. It may have been the case that GPs involved in our study already had a high level of knowledge about the issue of sick leave and work conditions, influencing this. Unfortunately, we did not test this beforehand, so no definitive conclusions can be drawn.

The role of general practitioners

Dutch general practitioners provide high-quality care, mostly in accordance with national guidelines[18]. General practice acts as a gatekeeper; almost all contacts are handled solely by the general practitioner. Moreover, GPs usually have a personal relationship with their patients because the care provided is embedded in the health care system to serve one's entire life. The medical responsibility of GPs is extensive, the many demands that are placed on them are intensive and their available time is limited and costly[16]. Many patients visit their GP because of problems that are psychological in origin, and at least some of these patients do not receive the help they need. It is often argued that the position of GPs in mental health care is one of being the observer and gatekeeper, with diagnosing and referral as their task. Complex interventions should accordingly not be the task of the already overloaded GP[19]. In most settings, GPs already cooperate with primary care psychologist and social workers, but this form of cooperation is not structural. The fact that policy makers decided to include treatment of primary care psychologist in basic health care insurance as from 2008 is promising. Furthermore, nurse practitioners may be able to deliver psychosocial interventions in primary care[20]. Nowadays, their tasks are mainly focussed on the care for chronic patients (e.g. diabetes, cardiovascular diseases).

Both the GP and OP ought to play an important and complementary role in the process of returning a patient to the workplace and to prevent long-term sick leave or disability. It is said

that during treatment, the GP is mainly focused on diagnosis and treatment of the mental health problem, whereas the OPs are mainly focused on return to work and working conditions[17;21]. Giving advice is one of the elements of the MISS. Perhaps this step needs fine-tuning towards work and working conditions. Communication and co-operation between OPs and GPs may be fundamental for improvement of care for patients having symptoms of SMD. However, realization in practice is unsatisfactory. In the Netherlands, all parties involved are concerned about this sub-optimal situation, and try to improve it[22].

Overall evidence

Very little evidence exists regarding the effects of training interventions for improving care of patients with stress-related mental health problems. We were the first to study such a particular intervention delivered by general practitioners, and the evidence base has to grow substantially before definitive conclusions can be drawn. The findings presented in this thesis are a first step and many of the issues discussed remain unclear. The results showed no evidence that the MISS was superior to UC on the total group level. However, subgroup analyses showed effectiveness and cost-effectiveness of MISS over UC, on days of sick leave for the patients that were actually diagnosed by their GP as having a SMD.

In this thesis, we explored possible impeding and stimulating factors within the patients under study, the intervention and the role of the GP. On top of that, we can compare our results with those in two other studies in the field of SMDs and sick leave. One study carried out in an occupational health care setting is in conformity with the positive results found in our subgroup[23]. In that study, patients were beforehand selected as having an adjustment disorder. The applied intervention programme was based on the same principles as the MISS, but execution was more extensive. Another study in primary care, in which social workers were trained to apply an activating intervention while GPs provided UC for patients in the other group, did not show positive results[24]. In this study, patients were diagnosed as suffering from emotional distress or minor mental disorders according to GPs and self-report. The results found in our subgroup, in addition to those found by Van der Klink et al[23], suggest that the MISS as an activating intervention is a promising approach for patients suffering from psychopathology which is sub-acute, not chronic and clearly related to stress (e.g. SMD, adjustment disorder, neurasthenia, nervous breakdown), but so far the MISS has not been demonstrated to prevent disability in patients with psychological problems convincingly. Differences between treatment groups regarding effectiveness on time to return to work were found, but not regarding symptom reduction. There is apparently little synchrony of change between symptoms and sick leave[25]. This suggests that the way forward may be a time-contingent and symptom-independent scheme, e.g. a focus on functioning and return to work instead of complaints[26]. This focus on functioning is embedded in the MISS. The fourth step, monitoring if the patient has moved towards an orientation on solutions, reflects this. And also the next step in the MISS, referral, was to be considered when no progress was being made on a time- contingent base. So ideally, if necessary the MISS should lead to more extensive treatment. Further development of the MISS may take into account an improvement of the monitoring abilities for GPs, and also include a more thoroughly stepped care program.

Further research

The research agenda on patients having SMDs with sick leave should include the evaluation of methods to define and assess disease and disability for both clinical and research applications[27]. Research should focus on more comprehensive nomenclature of psychological morbidity. Evidently, dimensions of distress, depression, anxiety and somatization are correlated. The role of distress in depression and anxiety versus distress as a distinct factor is a subject for debate on nomenclature. This is essential for defining patient subgroups in the primary care research setting. Variation in duration of symptoms, and symptom constructs based on a dimensional model must be acknowledged in operationalization of the diagnostic process. Additionally, in future research patients characteristics should be considered for fine-tuning the necessary elements of the MISS. Starting not only from well established diagnoses, but also from usual complaints and symptoms[28;29]. In other words, pathways to and from SMDs and sick leave should be examined. This can be done by a combined evaluation of factors involved within patients (severity of symptoms, coping, autonomy), and context-related factors (family, work, social network). Foremost, research on the fit for treatment of (core) dimensions of distress is crucial for the further development of elements within the MISS. Assuming the MISS could be the way out for preventing disability in patients with psychological problems implies fine-tuning. Which element needs revision for which subgroup of patients has yet to be determined. Considering these needs, only studying effectiveness with a randomised controlled trial seems insufficient. Also qualitative research on the above mentioned factors involved in SMD symptoms and sick leave is recommended.

Implications for general practice

Implications of our study for daily general practice are not completely straightforward. Many factors outside the direct scope of the GP, e.g. work related factors, presumably play a major role in the recovery process and for some patients a more extensive treatment is needed. Combined effort and co-operation with other caregivers in the field, like the OP, primary care psychologist and social workers may seem of best interest for everyone involved. Yet, also for the other caregivers there still is much to gain by the further development, identification and implementation of effective care for patients on sick leave having SMDs.

In case of SMD and the MISS, practice lies ahead of evidence base. Currently, government and company policy is aimed at an activating intervention for SMD. A common guideline for both GPs and OPs to manage work related mental health disorders was developed in 2006[17], and this guideline contains elements of the MISS. Furthermore, the information leaflet used in the MISS training is integrated in the official medical information system of GPs. Our subgroup analysis supports all these developments, in case a GP diagnosed a SMD. In conclusion, these developments in practice certainly are positive and worth structural support by training and education, since they reflect a step forward in a field that not yet has, but clearly needs, more well defined and structured care.

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Summary

1. Introduction

As stated in chapter 1, this study is carried out because patients and their care-givers have much to gain by the development and implementation of effective care for patients on sick leave having stress-related mental disorders (SMDs). Most people having SMDs with sick leave consult their general practitioner (GP) at an early stage. Currently, few evidence-based therapies exist to help patients to cope and to prevent sick leave, and general practice lacks a guideline with a structured treatment plan. We developed a minimal intervention to help GPs diagnose and treat patients having SMDs with sick leave.

2. Stress and coping in relation to common mental disorders and the MISS

In chapter 2, we argue that the concept of stress-related disorders does not fit the existing diagnostic classification systems (such as the DSM-IV and the ICD-10), but may be most applicable when no formal psychiatric disorders are diagnosable. It may be viewed as an important dimension of mental disorders that cuts across all established diagnostic categories. In the Minimal Intervention for patients having SMDs with Sick leave (MISS), GPs focus on the first stage of the breakdown. After the 'crisis' a patient experiences, patients need to regain control and start coping again. Otherwise, the long-lasting sick leave could have severe consequences like loss of employment, social marginalisation and permanent disability. Through the use of relatively simple, empowering interventions such as education, support, advice and homework assignments, the intervention specifically aims at damming avoiding tendencies and at promoting an active approach of psychosocial problems.

3. Design

Chapter 3 provides a description of the setting and design of our MISS, and confirms compliance with the requirements for a cluster Randomised Controlled Trial (RCT). Our hypothesis was that the MISS is more effective compared to usual care (UC) in reducing days of sick leave of these patients. Randomisation was at the level of GPs, they received the MISS training versus no training, in order to compare the MISS vs. usual care at patient level. Enrolment of participants took place after screening the source population, which comprised 20-60 year old primary care attendees. Enrolment criteria were: moderately elevated distress levels, having a paid job and sick leave for no longer than three months. Primary outcome measure after one year follow-up was lasting full return to work. Reduction of SMD symptoms was one of the secondary outcome measures. Forty-six GPs and 433 patients agreed to participate.

4. Effectiveness of the MISS

Chapter 4 presents the effects of our MISS versus UC. There was no evidence that the MISS was superior to UC within the total group on our primary outcome measure days of sick leave (HR 1.06, 95% CI 0.87 – 1.29). The median number of days on sick leave before return to work was substantial (MISS 96 days and UC 102 days). Subgroup analyses showed effectiveness of MISS over UC on days on sick leave for the subgroup, SMDs (HR 1.72, 95% CI 1.18- 2.51). The severity of symptoms reduced significantly in both groups during follow up. Nevertheless, a considerable amount of patients after 1 year still scored above threshold on the self-reported symptoms. Diagnosing SMD turned out to be less straightforward than we expected and the evidence-base on effectiveness of the MISS has to grow substantially before definitive conclusions can be drawn.

5. Cost-effectiveness of the MISS

Chapter 5 presents the cost -effectiveness of our MISS compared to UC. The economic evaluation was performed alongside our cluster RCT and conducted from both societal and company perspective with a follow up of one year. Outcomes were the number of sick leave days beginning from the first day of sick leave to 1-year thereafter, quality adjusted life years, resource use, investment costs and productivity loss costs.

In total, 192 (44%) complete cases were available. There were no significant differences in outcomes or costs. The incremental costs per day less of gross sick leave was €33, and per quality adjusted life years €76,046. The potential cost offset ranged from a loss of € 135 to a savings of € 1369. Results of sensitivity analysis were similar to the main findings for the total group. With respect to the SMD subgroup, cost-effectiveness of MISS over UC was indicated. Those in the MISS group incurred significantly less gross and net sick leave days than UC (mean gross difference 74.0 days, 95% CI 14.7 – 132.9). While the MISS was not associated with a superior clinical or economic impact than usual GP care for a heterogeneous population with symptoms of SMD, it may be a promising intervention for the subgroup, patients diagnosed with SMD.

6. Performance of the general practitioners

The aim of chapter 6 was to evaluate the potential differences between the MISS and UC in application of treatment-components. Elements in the MISS were: assignment of a correct diagnosis, providing information and advice, monitoring the symptoms and, if necessary, referral to more extensive care. Twenty-four GPs were randomly assigned to the MISS-group, 23 of whom completed the 11-hour MISS training. Information on application of the treatment components was derived from questionnaires filled in by both the GP and patients, and from the electronic medical record of the patient. Differences in favour of the MISS group were found for several elements of the MISS. A psychological diagnosis was more frequently diagnosed by the GPs in the MISS group than by the GPs in the UC group (78.1% versus 67.4%, p=0.020). Furthermore, the GPs in the MISS group more often used a mental health questionnaire (the 4DSQ) (16.1% vs. 1.3%, p=0.000), handed out information leaflets (28.3% vs. 10.8%, p=0.001) and knew how the patients are doing two months after baseline (76.4% vs. 65.7%, p=0.041). The treatment components advice and referral did not show significant differences between MISS and UC. In conclusion, GPs can be trained to successfully apply at least some of the elements of the MISS intervention.

7. Test- retest reliability of the PRIME-MD

In chapter 7, test-retest study of the Primary Care Evaluation of Mental Disorders (PRIME MD) is described. The PRIME-MD is one of the few instruments in primary care that actually diagnoses specific mental disorders according to the DSM criteria. One-hundred distressed patients (20-60 years old) who were on sick leave were interviewed, with one-week interval. Almost everyone (89%) received one or more diagnoses at both measurements, and there was fair total agreement (κ .27). The best agreement was found for more severe threshold disorders (major depressive disorder [κ .58], dysthymia [κ .57], and generalised anxiety disorder [κ .59]), while agreement for the sub-threshold disorders was not satisfactory (anxiety disorder not otherwise specified [NOS] [κ .30], minor depressive disorder [κ -.03], and somatoform disorder NOS [κ .11]). Mental disorders, as seen in primary care,

encompass important specific symptoms and clinical syndromes that vary in duration and severity over time, but they also encompass an admixture of somatic and psychological symptoms that do not match current diagnostic systems. This probably contributes to the overly inclusiveness of threshold disorders and the failure to adequately classify sub-threshold disorders with the PRIME-MD. In conclusion, diagnostic criteria in psychiatry need to be operationalised for use in primary care and require further evaluation.

8. General discussion

In chapter 8, some important issues and considerations covering the foregoing chapters were discussed. The findings presented in this thesis are a first step and many of the issues discussed remain unclear. The results showed no evidence that the MISS was superior to UC on the total group level. Subgroup analyses showed effectiveness and cost-effectiveness of MISS over UC on days of sick leave for the patients that actually were diagnosed by their GP as having a SMD. This suggest that the MISS as an activating intervention is a promising approach for patients suffering from psychopathology which are sub-acute, not chronic and clearly related to stress (e.g. SMD, adjustment disorder, neurasthenia, nervous breakdown), but so far the MISS is not *the* way out for preventing disability in patients with psychological problems. The research agenda on patients having (symptoms of) SMDs with sick leave should include the evaluation of methods to define and assess disease and disability, and patients characteristics should be evaluated for fine-tuning the necessary elements of the MISS. Considering these needs, only studying effectiveness with a randomised controlled trial may seem insufficient. Also qualitative research on the above mentioned factors involved in SMD symptoms and sick leave is recommended. Implications of our study for daily general practice are not completely straightforward, yet practice lies ahead of evidence base since some elements form the MISS already are implemented. And in conclusion, these developments in practice certainly are positive and worth structural support by training and education, since they reflect a step forward in a field that not yet has but clearly needs more well defined and structured care.

Samenvatting

Introductie

Huisartsen en hun patiënten kunnen veel baat kunnen hebben bij een effectieve behandeling voor surmenage (overspanning)[I] De meeste mensen die verzuimen van hun werk en overspannen zijn, gaan langs op het spreekuur van hun huisarts. Toch is er nog geen richtlijn beschikbaar voor huisartsen om mensen te helpen omgaan met hun problemen en om het ziekteverzuim te reduceren (of te voorkomen). Bedrijfsartsen hebben al wel een begeleidingsmodel tot hun beschikking[II], en deze is aangepast voor de huisartspraktijk: de Minimale Interventie Strategie voor Surmenage (MISS).

Surmenage en de MISS

In hoofdstuk 2 wordt uitgebreid ingegaan op het ontstaan en de beloop van surmenage. In geval van surmenage gaat het om symptomen van distress als een dimensie van psychische klachten. Distress kan licht of ernstig disfunctioneren veroorzaken, bovendien loopt een patiënt het risico op verergering of chroniciteit van de klachten. In de diagnostiek bij overspanning is het van belang om een onderscheid te kunnen maken tussen psychiatrische stoornissen (de meest voorkomende zijn depressieve stoornis en angststoornis), en de aanwezigheid van psychische problemen in het algemeen (distress), zonder dat er sprake is van een formele psychiatrische stoornis. In de MISS-training wordt huisartsen geleerd om dit onderscheid te maken met behulp van de Vierdimensionale Klachtenlijst (4DKL)[III]. Daarnaast wordt hen geleerd om alert te zijn op het eerste stadium van surmenage, de crisisfase. In deze fase hebben patiënten door hun behoefte aan rust de neiging om passief te blijven en de problemen op hun beloop te laten. Het is belangrijk dat patiënten inzien en accepteren dat het mis gegaan is, en weer grip proberen te krijgen op de situatie. Dit kunnen ze doen door te focussen op de problemen die de overspanning veroorzaakt hebben in plaats van enkel op de klachten, en door vervolgens te focussen op oplossingen voor deze problemen. Doen patiënten dit niet, dan lopen ze het risico om langdurig arbeidsongeschikt te raken. Door middel van een activerende interventie, met daarin voorlichting, ondersteuning, advies en huiswerkopdrachten wordt vermijding tegengegaan en een actieve aanpak van problemen aangespoord.

Onderzoeksopzet

In hoofdstuk 3 wordt de onderzoeksopzet beschreven. We wilden nagaan of onze MISS (kosten) effectiever is dan de gebruikelijke zorg door de huisarts in het reduceren van het aantal dagen ziekteverzuim en in het verminderen van de klachten. We hebben 46 huisartsen voor het onderzoek geworven en willekeurig verdeeld in een groep die een training in de MISS (n=24) gekregen heeft en een controlegroep die gebruikelijke zorg leverde (n=22). Volwassen patiënten (20-60 jaar) die bij de deelnemende huisartsen op het spreekuur waren geweest, kregen een screeningslijst toegestuurd met vragen over spanningsklachten (piekeren, lusteloosheid en gespannenheid), betaald werk en ziekteverzuim. Wanneer patiënten een vastgesteld niveau van spanningsklachten hadden,

I De diagnose ‘surmenage’ of ‘overspanning’ kent geen internationale equivalent, om de lading in de Engelse taal zo goed mogelijk te dekken is voor de term ‘stress- related mental disorder’ gekozen.

II NVAB (Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde) / J.J.L. van der Klink(red.) (2000). Handelen van de bedrijfsarts bij werknemers met psychische klachten. Richtlijnen voor bedrijfsartsen. Eindhoven: NVAB.

III Auteur B. Terluin. www.emgo.nl/researchtools/4dsq.asp

en daarbij hun werk verzuimden, werd hen gevraagd om mee te doen met een onderzoek naar spanningsklachten en ziekteverzuim. Dit betekent dat we niet alleen patiënten hebben geïncludeerd die de diagnose surmenage van hun huisarts hadden gekregen, maar een groep patiënten met spanningsklachten. De reden hiervoor is dat we nu konden meten of huisartsen die de training gevolgd hebben, psychische klachten ook beter gaan herkennen bij hun patiënten. De deelnemende patiënten werden telefonisch geïnterviewd en kregen vragenlijsten per post toegestuurd. De patiënten werden vervolgens na 2, 6 en 12 maanden opnieuw telefonisch geïnterviewd en kregen opnieuw vragenlijsten. De huisartsen kregen na 2 maanden een enquête over de diagnostiek en behandeling van elke patiënt. Er werden in totaal 433 patiënten geïncludeerd (227 in de MISS-groep en 206 in de controlegroep).

Effectiviteit van de MISS

Door de groep patiënten van wie de huisarts een training in de MISS heeft gehad te vergelijken met de groep patiënten van wie de huisarts de gebruikelijke zorg leverde, kan worden nagegaan hoe effectief de MISS is. Zoals in hoofdstuk 4 beschreven staat, hebben we geen bewijs gevonden dat de MISS superieur was ten opzichte van de gebruikelijke zorg in het verminderen van het aantal dagen ziekteverzuim (Hazard Ratio 1.06, 95% BI 0.87-1.29). De mediane duur van het ziekteverzuim was hoog: het middenpunt in de verdeling van het aantal dagen ziekteverzuim onder de deelnemers lag in de MISS groep op 96 dagen en voor de gebruikelijke zorg op 102 dagen. In de subgroep van patiënten met de diagnose ‘surmenage’ vonden we een statistisch significant verschil in verzuimduur tussen de MISS en gebruikelijke zorg (mediaan 97 dagen versus 170 dagen, Hazard Ratio 1.72, 95% BI 1.18-2.51), dat niet verklaard kon worden uit verschillen in leeftijd, geslacht of ernst van de klachten. De klachten verbeterden in beide groepen even sterk, maar aan het eind van het jaar had een substantiële groep patiënten nog steeds verhoogde symptomen van distress. De diagnostiek van surmenage bleek gecompliceerder dan op voorhand gedacht en definitieve conclusies over de bruikbaarheid van de MISS kunnen dan ook niet getrokken worden op basis van dit onderzoek.

Kosten effectiviteit van de MISS

Tijdens het MISS project is er eveneens een economische evaluatie uitgevoerd, vanuit zowel maatschappelijk- als bedrijfsperspectief. Dit staat beschreven in hoofdstuk 5. Er is gekeken naar het totaal aantal dagen ziekteverzuim gedurende het jaar volgend op de ziekmelding, levensjaren in goede gezondheid, het gebruik van middelen en diensten, investeringskosten en kosten door productiviteitsverlies. In totaal waren er 192 (44%) complete cases beschikbaar, en er zijn geen significante verschillen gevonden in uitkomsten en kosten tussen de MISS en de gebruikelijke zorg. De potentiële kosten en baten van de MISS reikten van een verlies van €135,- tot een besparing van €1369,-. Voor de subgroep van patiënten met de diagnose ‘surmenage’ leek de MISS kosteneffectief: patiënten in de MISS groep hadden een significant lager aantal dagen verzuim in het jaar waarin ze gevolgd werden (gemiddeld verschil 74 dagen, 95% BI 14.7-132.9 dagen). Voor deze subgroep lijkt de MISS een veelbelovende interventie te zijn, terwijl er geen verschillen in uitkomsten gevonden werden voor de gehele groep van patiënten met stressgerelateerde psychische klachten.

De MISS-behandeling in de praktijk

De MISS-huisartsen (n=24) kregen een cursus van in totaal 11 uur, de controle huisartsen (n=22) gaven hun patiënten de gebruikelijke zorg. Informatie over diagnostiek en daadwerkelijke uitvoer van verschillende behandelstappen (het geven van informatie en advies, monitoren en eventueel verwijzing) door de huisartsen is geëvalueerd met behulp van gegevens gekregen van zowel de huisartsen als de patiënten, en met behulp van gegevens uit het elektronisch medisch dossier. Verschillen ten gunste van de MISS-huisartsen werden gevonden voor meerdere behandelstappen. Zij diagnosticeerden vaker een psychische klacht (MISS 78.1% versus UC 67.4%, p=0.020) en gebruikten vaker de Vierdimensionale Klachtenlijst (4DKL) (16.1% versus 1.3%, p=0.00). Bovendien gaven de MISS huisartsen vaker voorlichtingsmateriaal mee (28.3% vs. 10.8%, p=0.001) en waren ze beter op de hoogte van de gesteldheid van een patiënt na 2 maanden (76.4% vs. 65.7%, p=0.041). Wat betreft het geven van adviezen en verwijzingen naar meer gespecialiseerde zorg zijn er geen verschillen gevonden tussen huisartsen die de MISS gevolgd hebben en huisartsen die gebruikelijke zorg leverden. Wij concluderen aan de hand van deze gegevens dat huisartsen met succes getraind kunnen worden om (in ieder geval een aantal) behandelstappen van de MISS toe te passen.

Test- hertest betrouwbaarheid van de PRIME-MD

In hoofdstuk 7 wordt de betrouwbaarheid van de diagnostiek met behulp van de 'Primary Care Evaluation of Mental Disorders' (PRIME MD)[IVV] op basis van een test-hertest onderzoek beschreven. The PRIME-MD is een van de weinige vragenlijsten voor de huisartspraktijk, die specifieke diagnoses[VI] stelt op basis van de internationaal geldende criteria voor psychische stoornissen. Honderd patiënten met spanningsklachten en ziekteverzuim werden, met één week tussentijd, tweemaal geïnterviewd om te kijken hoe betrouwbaar de diagnostiek met behulp van de PRIME MD is. Bijna iedereen (89%) kreeg één of meerdere diagnoses volgens de PRIME-MD, de overeenstemming tussen beide meetmomenten werd als laag beoordeeld (κ .27)[VII]. De beste overeenkomst tussen beide meetmomenten werd gevonden bij de zwaardere stoornissen (ernstige depressieve stoornis [κ .58], dysthymie [κ .57], en gegeneraliseerde angststoornis [κ .59]). De overeenstemming tussen beide meetmomenten was niet zo goed bij de mildere stoornissen (angststoornis niet anders omschreven [κ .30], milde depressieve stoornis [κ -.03], en somatoforme stoornis niet anders omschreven [κ .11]).

Het type psychische klachten dat de huisarts tegenkomt op zijn spreekuur is zeer divers, en onze voorselectie op spanningsklachten en ziekteverzuim heeft wellicht zijn weerslag gehad op de resultaten van onze test-hertest. Er zijn aanwijzingen dat de PRIME-MD onvoldoende in staat is om onderscheid te maken tussen 'geen diagnose', een 'lichte stoornis' of een 'zwaardere stoornis', terwijl dit voor een eventuele behandeling wel een belangrijk onderscheid is. Een huisarts heeft te maken met zowel specifieke symptomen en klinische

[IV] Spitzer RL et all. Utility of New Procedure for Diagnosing Mental Disorders in Primary-Care - the Prime-Md-1000 Study. Journal of the American Medical Association 1994;272:1749-56.

[V] Zitman, F. G. & Van Wetten, M. L. (1995). PRIME MD. Werkboek voor de arts, DSM-IV versie.

[VI] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM). Washington: 1952.

[VII] [4]Kappa (κ) scores van .80 en hoger worden als 'zeer goed' beoordeeld, hoger dan .60 als 'goed', kappa's tussen .41 and .60 als 'voldoende'. Een kappa tussen .21 and .40 wordt als 'matig' en scores daaronder als 'slecht'.

stoornissen, passend in de internationaal geldende criteria voor psychische stoornissen, als meer 'alledaagse psychische klachten', waarbij een mix van a-specifieke symptomen zichtbaar is. Onze conclusie is dat de diagnostische criteria, zoals gebruikt in de PRIME-MD, nog meer aangepast moeten worden voor een betrouwbaar gebruik in de huisartspraktijk.

Discussie

In hoofdstuk 8 worden ten slotte een aantal belangrijke punten besproken, aansluitend op de totale onderzoeksopzet en -uitvoer. Voor zover bekend, is dit de eerste studie naar de effectiviteit van een strategie voor huisartsen om patiënten met spanningsklachten en ziekteverzuim te helpen omgaan met hun problemen en om het ziekteverzuim te reduceren. Er is geen effect gevonden voor de totale groep van patiënten, niet op het ziekteverzuim of klachten en niet op de kosten. Subgroep analyses lieten een effect zien op ziekteverzuim en kosten voor de groep patiënten die de diagnose 'surmenage' hadden gekregen van hun huisarts. Dit suggereert dat de MISS, als activerende interventie strategie, een veelbelovende behandeling is voor deze patiënten, maar niet voor de gehele groep patiënten die spanningsklachten heeft, ongeacht de diagnose. Verdere evaluatie van methoden om spanningsklachten beter te definiëren is nodig om meer definitieve uitspraken te kunnen doen over de werkzaamheid van de MISS. De verschillen en overeenkomsten in de heterogene groep van patiënten met spanningsklachten zullen nader bestudeerd moeten worden om de elementen van de MISS verder te ontwikkelen en mogelijk effectiever te maken. Hiervoor is meer en eveneens kwalitatief onderzoek wenselijk, om het theoretisch concept, onder andere rondom de diagnostiek van spanningsklachten binnen de huisartspraktijk, te verstevigen. Uit al het bovenstaande komt naar voren dat er geen ondubbelzinning en duidelijk advies voor de praktijk van het gebruik van de MISS mogelijk is. Echter, in de praktijk worden al enkele elementen uit de MISS toegepast. Vanuit een samenwerking tussen het Nederlands Huisarts Genootschap (NHG) en de Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde (NVAB) is in 2005 de Landelijke Eerstelijns Samenwerkings Afspraak (LESA) "Overspanning"[VIII] gepubliceerd. Deze LESA bevat adviezen die we in het MISS-project hebben onderzocht. Bovendien is de informatiefolder voor overspannen patiënten, die de huisartsen in de het kader van het MISS-project gebruikten, bewerkt tot een tweetal NHG patiëntenbrieven, die geïntegreerd [IX]zijn in het Huisarts Informatie Systeem (elektronisch dossier). Deze initiatieven en ontwikkelingen in de praktijk zijn zeer zeker positief, en de moeite waard om verder uit te werken. Training en onderwijs in een activerende benadering van spanningsklachten markeren een stap verder op een voor de huisartspraktijk deels nog onbekend terrein.

[VIII] ACM Romeijnders et all. Landelijke Eerstelijns Samenwerkings Afspraak Overspanning. Huisarts en Wetenschap 2005;48(1):20-3.